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AGARD CONFERENCE PROCEEDINGS No.415

Biochemical Enhancement of Performance

NORTH ATLANTIC TREATY ORGANIZATION

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NORTH ATLANTIC TREATY ORGANIZATION

ADVISORY GROUP FOR AEROSPACE RESEARCH AND DEVELOPMENT

(ORGANISATION DU TRAITE DE L'ATLANTIQUE NORD)

AGARD Conference Proceedings No.415

BIOCHEMICAL ENHANCEMENT OF PERFORMANCE

Papers presented at the Aerospace Medical Panel Symposium held in Lisbon, Portugal from 30 September to 2 October 1986.

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The mission of AGARD is to bring together the leading personalities of the NATO nations in the fields of science and technology relating to aerospace for the following purposes:

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Published March 1987

ISBN 92-835-0414-3

Printed by Specialised Printing Services Limited
40 Chigwell Lane, Loughton, Essex IG10 3TZ

PREFACE

It has been repeatedly pointed out that the performance demands placed on military personnel, especially aircrew, are exceeding the ability of the operator to perform them. Advances in engineering help by providing the operator better information displays, easier to operate equipment, and work places which are more suited to the physical characteristics of the man. Training, especially simulator activities, provides the operator with an enormous familiarity with the equipment he is to operate and his own ability to operate it. However, there is a limit to the benefits to be accrued to the operator by these technologies.

A recent innovation in the attempts to enhance operator performance is in the direction of direct intervention with the operator's basic physiology by the use of nutritional and pharmaceutical agents. The objective is to enhance the operator's performance by increasing his ability to receive, process and act on the very large amounts of information presented to him.

This symposium was the first attempt of the AMP to present to the member nations recent work in this important area. Papers considered both basic research and operational aspects of the use of pharmaceuticals and nutritional supplements to enhance performance.

* * *

On a souvent mis l'accent sur le fait que les performances exigées du personnel militaire, en particulier, du personnel navigant, dépassent les possibilités humaines. Certes, grâce aux progrès techniques réalisés, l'opérateur dispose d'une meilleure visualisation des informations, d'un équipement plus facile à utiliser et d'installations plus adaptées à ses caractéristiques physiques.

L'entrainement, en particulier, les exercices sur simulateur permettent à l'opérateur d'être très familiarisé avec l'équipment qu'il doit utiliser et augmentent ses capacités d'adaptation. Cependant le bénéfice que l'opérateur peut tirer de ces technologies est limité.

On s'est efforcé récemment d'accroître les performances de l'opérateur par une innovation qui consiste à agir directement sur la physiologie de base de l'opérateur en utilisant des agents nutritionnels et pharmacologiques. Le but recherché étant d'augmenter les performances de l'opérateur en améliorant sa capacité de réception et de traitement des très nombreuses informations qui lui sont présentées et sa capacité d'action en fonction de ces informations.

Le présent Symposium a donné pour la première fois au Panel de Médecine Aérospatiale l'occasion de faire connaître aux pays-membres les récents travaux qui ont été effectués dans ce domaine important. Les mémoires présentés portaient à la fois sur les questions de recherche fondamentale et sur les aspects opérationnels de l'utilisation des produits pharmaceutiques et adjuvants nutritionnels propres à accroître les performances.

AEROSPACE MEDICAL PANEL

TECHNICAL PROGRAMME COMMITTEE

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PANEL EXECUTIVE

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*Presented during informal briefings and discussion period on "Phobic Reactions in Experienced Aviators" on 2 October 1986.

Technical Evaluation Report
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Introduction

One hundred years ago it was adequate to select military personnel based primarily on their physical characteristics and state of health. With time, as military equipment became more complex, selection procedures became more sophisticated and other factors such as mental abilities, hand-eye coordination and attitude characteristics were included. Training became more important and at times was specifically tied to certain types of equipment and duties.

Research began to assume a more important role in arriving at solutions to problems associated with man operating in difficult military environments. Early research was aimed at defining man's tolerances and limitations in those environments and offering recommendations for increasing his tolerance. The recommendations centered around training, acclimatization, nutrition, operational scheduling and equipment improvements. Human factors engineering assumed an important role. As equipment became more and more complex, problems associated with the fit (both physical and mental) of the operator to his equipment came to the fore. A great deal of research was, and is, being conducted to solve those problems and assure the best interaction between man and his weapon system. However, one conclusion of the Technical Evaluation Report for the Aerospace Medical Panel Symposium on "Human Factors Considerations in High Performance Aircraft" held in 1984 was that the operator of high perofrmance weapon systems is nearly saturated and that in future combat aircraft the mental and physical workload of the operator must be reduced in order to enhance his battle management and decision making role.

Some attempts were made during WWII to look at the biochemical and physiological makeup of the military person with the objective in mind that individuals could be selected for certain types of military duty based on certain biochemical and physiological characteristics which would ideally suit him for that job. This approach did not come to great fruition but was fundamental in providing the basis for the current thought that man's capabilities can be greatly extended by altering his basic chemistry. It appears that while selection, training, human engineering and equipemnt modification still offer possibilities for human operator enhancement, the giant strides in performance enhancement will come by altering the operator himself at the most fundamental cellular level.

The Aerospace Medical Panel has recognized the need to consider these newer approaches to the operator performance problem and provided a program in Lisbon, Portugal during 30 September to 2 October 1986 entitled "Biochemical Enhancement of Performance."

Theme

The main concern of this symposium is that the operator of today's weapon systems is deluged with information from a variety of sources and his ability to receive, process and act on that information, which has finite limits, is being overtaxed. This "limited" ability of the operator in turn limits the effectiveness of the weapon system he is operating. Full effectiveness of the weapon system therefore may never be achieved. This symposium considered the possibility that man's performance can be enhanced by a variety of techniques, including nutritional supplements, biochemicals and natural biological products. The papers presented represent the latest scientific thinking in this area.

Purpose and Scope

The purpose of this symposium was to provide the member nations with the latest scientific information concerning new and innovative possibilities for enhancing the operator's performance in modern weapon systems. The papers presented considered unique, and perhaps, unorthodox, means to provide the enhancement.

Because of the nature of the research in this emerging area, some of the work presented was of a rather exploratory nature and much of it was confined to research on animals. As additional research is performed, and more information becomes available concerning the possibilities for performance enhancement, more research will be done with human subjects and thus be more applicable to aerospace problems. The participation of scientists from several disciplines provided a multifaceted aspect to the sessions which included clinical, psychological, physiological and biochemical techniques. Nutritional and pharmacological studies predominated. Currently, drugs seem to offer the most readily convenient approach to study of this problem. Authors came from academic, military, government and clinical laboratories.

Symposium Program

The program consisted of three sessions spread over two days. A keynote address preceeded the sessions. There was no particular division of papers by session except that two papers dealing with enhancement through use of tyrosine supplementation were presented first. A third "nutrition" paper (effects of acety-dl-leucine) and a fourth which considered the use of tryptophan as a sedating aid were presented in Sessions II and III. The remaining seven papers concerned research directed toward the use of

pharmacological agents for enhancing performance or for modifying physiological and biochemical functions, which in turn had an influence on behavioral, physical or mental performance.

The papers, in brief, were as follows: The keynote address presented a review of factors which may alter performance. Optimum work-rest regimens were considered important for adequate performance. Performance varies with time of day (circadian rhythm) and as a function of time on duty. Judicious scheduling of duty times, time of day and rest (sleep) periods will provide best performance. The use of hypnotics in the Falkland campaign did not provide clearcut evidence of enhanced performance.

Session I consisted of two papers. Both were concerned with the effects of nutritionally supplied, or supplemented, tyrosine on performance. One paper provided information on the biochemical and physiological effects in an animal model. The second paper provided results of studies of humans exposed to stressful conditions with and without a tyrosine supplement.

Session II was concerned with the effects of various pharmacological agents in animals and man. These studies were clinically as well as physiologically oriented. One paper considered the effects of leucine (an antivertiginous candidate) on the vestibulo-occular reflex. There were five papers in this session.

Session III contained four papers, one of which presented information on pacemaker control of circadian rhythms and the relation of rhythms to performance. The remaining three papers presented results of studies of the effects of drugs on performance of military personnel in various environments and under various military operational situations. One of these provided tryptophan as a possible sleep enhancer.

Technical Evaluation

The objective of this symposium was to present to the AGARD community the latest scientific thinking and results concerning biochemical means of enhancing aircrew performance. The content of the symposium presented the results of work in nutritional enchancement, enhancement by the use of various drugs and enhancement by manipulation of regulatory centers. By far, most of the work presented was focused on enhancement by use of pharmaceuticals.

There were four papers which considered the effects of nutrition or nutritional supplements on performance enhancement. Supplementation with tryptophan, which was considered by the author to be a "non-sedating" sleeping aid, increased sleeptime of military personnel in an airlift operation and thereby enhanced performance in some memory and reaction time tests after arrival at the new destination.

Acetyl-dl-leucine is, among other things, an antivertiginous agent. Since vertigo is a condition which may affect the operator's ability to receive visual information, the authors decided to test the effect of leucine on the vestibulo-occular reflex. Leucine had no effect on the characteristics of the reflex, which indicates that its use as an antivertiginous agent will not impair visual information processing.

Tyrosine is a precursor of the catecholamine neurotransmitters dopamine and norepinephrine. Two papers considered the effects of tyrosine supplementation on performance in rats and military personnel. In one study it was determined that tyrosine protected rats from adverse effects of stress. In the other study, military personnel were subjected to altitude and cold stress. When tyrosine was given, the authors state that the adverse effects of cold and altitude on performance, symptoms and mood states were largely erased or minimized. Information processing, vigilance and reaction time were enhanced by typrosine. The beneficial effects became more apparent as the stresses became greater.

Several authors considered the possibility that performance is enhanced when sleep during difficult or prolonged operations is aided through the use of pharmaceuticals. However, one author pointed out that the use of hypnotics to enhance sleep may also have detrimental residual effects, as indicated by psychometric tests, which showed a deterioration in mental performance when subjects were tested after awakening from drug-aided sleep.

A clinical study of a new substance, delta-sleep-inducing-peptide (DSIP) produced results which, if they can be repeated by others, show that sleep is profoundly enhanced without any adverse effect of the peptide. Mental performance (memory function, arithmetic, learning) and visual judgement improved significantly. Mood states and mood status also improved.

Temazepam was used as a sleep aid in a study of aircrew involved in surge operations. Sleep was of longer duration and higher quality in daytime aircrews receiving temazepam. However, performance on simulator missions was no different than perofrmance when a placebo was given.

A new stimulant drug was under evaluation for possible use in humans. These workers state that in rhesus monkeys the drug had a marked anti-sleep effect without any disturbance of sleep pattern and without side effects on vegetative and behavioral functions.

A comprehensive study of several types of drugs on cognitive function (learning, working memory) and on reactions to stress and hypoxia was performed in rats. In brief, none of the drugs tested had any effect on information processing and reaction time under normal conditions. However, several types of drugs were effective in offsetting the deleterious effects of stress and hypoxia on cognitive function. Two agents in particular, nemodipine and ipsapirone, were effective.

The last study to be summarized here is one in which performance is related to sleep-wake patterns and circadian rhythms. The pacemaker or center for control of sleep-wake cycles can be manipulated by several techniques including light-dark cues and chemical agents. The authors show clearly the relationship of performancae to phase of the daily cycle and their data indicate that if performance is to be maintained in difficult or unusual work-rest schedules or in prolonged operations, work should be matched to the proper phase of the cycle. The authors provide a variety of ways in which periodicity can be altered.

This brief summary of the presented papers points out the variety of approaches used by the authors. The studies utilized animals and man, were performed in the laboratory and the field, and employed a variety of techniques and agents in their attempts to enhance performance. One consistency was that none of the studies explored basic mechanisms, a necessary condition for further development of agents at the membrane or cellular component level of the neurone.

The basic objective of the symposium, which was to deal with "basic research studies and the operational use of biochemicals to enhance performance" was therefore not completely achieved.

Some finding raise questions which should be explored further. For example, temazepam enhanced sleep in aircrews performing surge operations, but did not improve simulator performance over aircrews receiving placebo. In another study, tryptophan enhanced sleep of personnel in an airlift operation and also enhanced performance. Why the difference? Possibly the answer lies in the different mechanism of action of the two agents. This again points out the importance of encouraging research of cellular neurochemistry.

Conclusions

The human operator in advanced weapon systms is deluged with great amounts of information. He has almost reached the point where he cannot perceive and process that information, make appropriate decisions, then respond in a timely manner.

More effecient ways of presenting visual information to the operator, the increased use of other sensory modalities to receive information, an ordering or prioritization of information presentation, and perhaps other hardware or procedural innovations can help the operator, but the essential human operator's limitations still exist.

New, and perhaps unconventional approaches to enhanced operator performance must be explored if the operator is not to be rendered ineffective as the next generation of more complex and sophisticated weapon systems is placed in the inventory.

One possible approach for increasing operator effectiveness is to consider "altering" the operator in a reversible way, so that his performance in enhanced significantly.

Currently, this approach is being explored in a rather conventional way. Pharmaceuticals, especially, are used to promote sleep when crews must be on difficult work-rest regimens; to aid the operator to remain alert during prolonged operations; to alleviate the adverse effects of harsh environments, etc. Nutritional supplements are being explored to promote sleep and to provide precursors of neurotransmitters. Intervention of regulatory centers through the use of chemicals to place the operator in a more appropriate phase of his biological cycle, thereby increasing his effectiveness in shift work operations is being explored.

A more "unconventional" approach to enhancing operator performance is by altering, reversibly, the responsiveness of the neurone. The techniques and tools are avialable to explore the possibilities for altering membrane function, controlling neuro- transmitter concentrations and activites, altering receptor number and responsiveness, enhancing transmission or conductivity, and many others. These options should be pursued vigorously.

Recommendations

The Aerospace Medical Panel should encourage research aimed at enhancing operator performance by altering neurone responsiveness. This approach has the potential for making great strides in altering human operator performance. Further symposia should be convened at regular intervals to follow progress being made in this area of research. Basic research should proceed in parallel with work on more conventional means for enhancing performance, such as the use of currently available pharmaceuticals and nutritional supplements. Both approaches should provide dividends in terms of increased effectiveness of human operator and therefore the weapon system itself.

KEYNOTE ADDRESS

Enhancement of Performance: Operational Considerations

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The enhancement of performance by pharmacological or biochemical means cannot be the sole approach to maintaining the effectiveness of personnel during intensive and sustained operations. Such agents may help to preserve sleep or to increase wakefulness, but they can only be used effectively when attention has been directed to optimising the work and rest pattern or, if this is not possible, anticipating the difficulties which are likely to arise. Indeed, the characteristics of duty periods influence performance and it may be possible to avoid patterns of work which lead to difficulties, include features in the schedule which may alleviate the situation and identify the periods of duty which are likely to cause difficulty. It is only against this background that hypnotics to preserve sleep and stimulants to enhance alertness may prove useful.

Optimum Pattern of Work and Rest

The main factors which influence performance during a duty period are the time since sleep, the time of day and the time on task. Time of day and time on task are particularly important. Time of day is a sinusoidal variation in performance related to circadian rhythmicity of the individual, whereas performance related to time on task rises during the first few hours of a duty period, returns to baseline about five hours later and then declines rapidly levelling off about 12-16 hours after commencement of duty. These two factors interact with each other. Performance during a 16 hour period of duty which commences around 0200 hours will be fairly well maintained as the fall in performance associated with a long period of work will not coincide with the fall in performance overnight, whereas a similar period of duty commencing around 1400 hours will lead to marked deterioration in performance. The latter adverse juxtaposition of time of day and time on task is relevant to overnight work which is, of course, essential in sustained air operations.

Now what can be done to improve performance if such an adverse interaction cannot be avoided? The first possibility is the use of short periods of sleep before long periods of work, or naps during the work period. Anticipatory sleeps of four hours in duration can be very effective, and such sleeps can be reinforced by hypnotics. Naps of an hour or so may also help, but their effect is probably limited, and more information is needed on whether naps can be used effectively. It is, nevertheless, important to appreciate that the arrangements for duty can have a profound effect on performance, and that strategies such as periods of sleep may be very relevant (Borland et al 1986, Nicholson et al 1985).

Preserving Sleep

To preserve sleep under difficult circumstances hypnotics are probably essential. The most relevant property of such drugs is the persistance of their effect which must be such as to provide sleep for the desired period but be free of residual effects on awakening and of accumulation on daily ingestion. It must also be adequately absorbed.

Maintaining Wakefulness

The potential role of stimulants in air operations remains uncertain. Three groups of drugs are of interest. They are dopamine agonists, adenosine antagonists and serotonin uptake inhibitors. The usefulness of these drugs in sustaining vigilance can be ascertained by their ability to increase wakefulness overnight, to improve performance overnight, and to increase alertness during the day. There is a variety of drugs with different mechanisms which increase alertness, and it remains to be seen whether they can be used effectively in sustained operations.

South Atlantic Campaign

It is with this background that we can now consider the approach which was used with the long range transport aircrew during the South Atlantic campaign (Baird et al 1983, Nicholson 1984). The aircraft were based on Ascension Island and there were no forward airfields. Some missions involved return flights of 6,800 miles with multiple air-to-air refuelling operations. The scenario led to an unusual pattern of work and rest with 36 hour periods of duty covering two nights and an intervening day. Changes in the operational scenario were not possible and it was essential that the rest periods between operations were used effectively. In this context we used the hypnotic temazepam (Normison-Wyeth).

Conclusions

Maintaining the effectiveness of aircrew during intensive and sustained air operations requires knowledge from many disciplines. We must understand how the performance of individuals is modified by unusual patterns of work and rest and how deterioration in performance can be limited by the use of short periods of sleep. A detailed understanding of drugs is needed and how they can be used either to preserve sleep or maintain vigilance. The initial approach must be to optimize the work pattern or at least the pattern of rest. The most effective approach at present is likely to be the use of short periods of sleep either before or during the missions and to ensure restful sleep between operations by the use of a hypnotic. At present the role of stimulants is less certain. Caffeine is used widely and is effective, but drugs which modify monoaminergic transmission require a much greater understanding than we have today of their pharmacological effects on the central nervous system and their effects on performance, both advantageous and adverse.

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ENHANCEMENT OF PERFORMANCE: OPERATIONAL CONSIDERATIONS

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The enhancement of performance by the use of drugs is unlikely to be the sole solution to the problems of sustained air operations. Drugs are a means by which alertness can be maintained either by preserving sleep or by increasing alertness, and they can only be used effectively when attention has first been directed to optimising the work and rest pattern of the schedule, or if this is not possible, by anticipating the difficulties which are likely to arise. The question of the potential role of pharmacological agents in air operations is in three stages. The characteristics of duty periods which influence performance must be understood first of all, and with this information it may be possible to avoid patterns of work which inevitably lead to difficulties, or include features in the schedule which may alleviate the situation. However, in the operational situation we are likely to have to deal with a work and rest schedule that cannot be modified, and under these circumstances it is important to identify the periods of duty which are likely to cause difficulty. Against this background we are able to look at the use of hypnotics to preserve sleep and of stimulants to enhance alertness.

In the management of intensive and sustained air operations we are almost certainly dealing with irregularity of work and rest, and there are two broad aspects which we must consider. First of all factors which influence performance. The main factors which influence performance during a duty period are the time since sleep, the time of day and the time on task, and it would appear that time of day and time on task are particularly important. The influences may be modelled in the following way. The time of day is a sinusoidal variation in performance, whereas performance related to time on task rises about 5 hours later and then declines rapidly, levelling off around 12 to 16 hours after the onset of the duty period. Clearly time of day and time on task may interact with each other and the extremes of the interaction occur when a long period of work, say 16 hours, begins at 2 o'clock in the afternoon as the deterioration in performance coincides with the nadir related to the circadian rhythm. This is particularly relevant to working overnight and of course this is likely to be inevitable in sustained air operations.

Now, what can be done to improve performance if such an interaction is inevitable? There is the possibility of using short periods of sleep before long periods of work, or including naps during the work period. Anticipatory sleeps of about 4 hours can be very effective and vigilance may be improved and the anticipatory sleeps may be reinforced by hypnotics. Naps may also help, but we probably need more information on their effect on performance. It is well established that naps after overnight periods of sleep loss reduce drowsiness during the day at least as shown by multiple sleep latencies, but it would appear that naps once the performance has deteriorated, are likely to be less effective, and may indeed have very little effect on vigilance. The conclusion is that the schedule itself and the arrangements for duty can have a very profound effect on performance, and that strategies which avoid sleep are likely to be more effective than attempts to reverse low levels of performance.

HYPNOTICS

Now we come to the question of preserving sleep. The pharmacokinetic profile of an hypnotic is an important consideration as their most relative property is persistence of effect. It is important that an hypnotic should be adequately absorbed, free of residual effects after the projected period of sleep and free of accumulation on repeated ingestion. Hypnotics can be of great help in air operations and their use in the South Atlantic Campaign will be reviewed later. Meanwhile it is important to be familiar with the activity of hypnotics, and the way in which they may be used.

Duration of activity depends on absorption, distribution and elimination. The rate of absorption determines onset of action, since hypnotics penetrate the blood-brain barrier easily. Rapid absorption is associated with a quick onset of action whereas with slow absorption the desired effect may be attenuated or even absent. An adequate rate is necessary if a drug is to be used as an hypnotic, whereas slower absorption may be more appropriate for the treatment of anxiety, where a sustained effect with minimal initial drowsiness is sought.

After absorption an hypnotic is distributed to the blood and to highly vascular tissues such as the brain, heart, lung and liver, and peripherally to tissues of lesser vascularity such as voluntary muscle. The initial fall in the plasma concentration may be quite marked and this relates primarily to the distribution of the drug, whereas the latter part of the fall relates to elimination by metabolism and by excretion.

In general, as hypnotics cross the blood-brain barrier with ease, a drug has a particular pharmacodynamic effect as long as its plasma concentration remains above a certain level. If this level is within the phase which predominantly represents distribution and this part of the decay is rapid, then the duration of action will be short, but if the level is within the elimination phase, which is slower than the distribution phase, it may be much longer. Thus distribution as well as elimination influences duration of activity, and so a relatively short duration of action may be attained with

a single dose of a drug which is not rapidly eliminated.

The influence of distribution on plasma concentration is important, and it follows that using the elimination half-life alone to indicate duration of action can be misleading. The elimination half-life may provide a relative estimate of duration of action when the drugs in question have comparable absorption and distribution, or, as with some rapidly eliminated drugs, when elimination is by far the dominant feature of the plasma decay, assuming again that they are absorbed in a similar manner.

The various hypnotics available may be considered in two broad categories. Some have a pharmacokinetic profile with a clear biexponential decay in which the parts played by distribution and elimination in the decline in plasma concentration are clear, and some have an essentially monoexponential decay. The duration of action of drugs which have a clear biexponential profile depends on distribution as well as elimination, and with some of these drugs it is relatively short because they have a marked distribution phase. Nevertheless, continued nightly ingestion may lead to accumulation of a slowly eliminated metabolite. It is for these reasons that a persistent effect may only be avoided when such drugs are used occasionally.

The group of hypnotics with an essentially monoexponential decay profile has a wide spectrum of elimination rates, and this provides a variety of durations of action. The distribution phase may not play a significant part in the fall in plasma concentration for those drugs which are slowly eliminated, but it may contribute to the fall in plasma concentration for those which are rapidly eliminated, though in each the elimination phase is likely to be the dominant factor in determining the plasma decay.

Clearly, slow elimination of parent compounds or of metabolites is disadvantageous if drugs are to be used on a nightly basis, and freedom from daytime effects is sought. However, a minor alteration in chemical structure may avoid this problem. For example, temazepam has a distribution phase similar to that of its parent compound, diazepam, but has a mean elimination half-life of around 8 h and does not have a more slowly eliminated metabolite. Thus, residual sequelae and accumulation on daily ingestion of temazepam are highly unlikely unless inappropriately high doses are used. The profiles of diazepam and temazepam illustrate the parts played by distribution and elimination of parent compounds and their metabolites, and show that both factors must be borne in mind when the activity of any drug with a biexponential decay is under consideration.

Drugs which for all clinical purposes have a monoexponential profile can be divided conveniently into two groups: (a) those which are slowly eliminated and in which accumulation occurs on a continued nightly ingestion; and (b) those which are rapidly or ultra-rapidly eliminated. The former group includes flurazepam and chlorazepate with their metabolites, desalkyflurazepam and desmethyldiazepam, respectively. Ingestion is likely to lead to a persistent effect, but this may be useful clinically as with chlorazepate in the treatment of insomnia with an anxiety component. Tolerance, at least subjectively, may develop to drugs which accumulate, and unwanted drowsiness may only be experienced early on in the course of therapy, but such subjective impressions do not necessarily imply absence of daytime effects.

There is now much interest in rapidly eliminated drugs, and several are available or may become available in the near future. Those with mean half-lives of around 2 to 3 hours (midazolam, triazolam and zolpidem) could be appropriately described as 'ultra-rapidly' eliminated, while those which have mean elimination half-livew of around 5 hours (brotizolam and zopiclone) could be usefully referred to as being rapidly eliminated. Rapidly and ultra-rapidly eliminated hypnotics in appropriate doses are free of residual effects the next day and of accumulation on continued nightly ingestion, but the rapidly eliminated drugs have the potential to sustain sleep, whereas this is less likely with the ultra-rapidly eliminated hypnotics. Compounds like brotizolam and zopiclone are also more likely to sustain sleep than drugs which have a marked distribution phase.

An hypnotic may be used to shorten sleep onset when there is difficulty in falling asleep, to reduce nocturnal wakefulness, or to provide an anxiolytic effect during the next day when insomnia is accompanied by a marked element of anxiety. The purpose of an hypnotic is to meet one or more of these clinical problems, though a useful compound may meet only one criterion. There also arises the question of what improvement in sleep is required to constitute efficacy. This is uncertain, but statistical evidence of a beneficial effect on sleep obtained in an appropriate group of subjects would indicate the lower dose of the recommended dose range. With this approach, the use of unnecessarily high doses in some subjects, if not many, will be avoided, and the relevance of dose will be emphasised.

In general, hypnotics are adequately absorbed and so most are useful for difficulties in sleep onset. However, some drugs which may be used as hypnotics are slowly absorbed, e.g. oxazepam and particularly loprazolam. It must also be realised that some hypnotics are available in alternative formulations which may have different rates of absorption, an example is temazepam. With the soft gelatine capsule formulation (Normison-Wyeth) the drug is adequately absorbed, with a mean delay to peak plasma concentrations of less than 1 hour. This formulation in the dose range 10 to 20 mg is useful for difficulties with sleep onset. However, in other formulations the drug may be more slowly absorbed. A higher dose may be used in an attempt to produce an immediate effect and this may lead to residual effects. On the other hand, some hypnotics are absorbed very rapidly indeed. An example is midazolam in which peak plasma concentrations may be reached in less than half an hour after ingestion, and the advantage of very rapid absorption is that a very

low dose may be quite adequate for difficulties with sleep onset.

A reasonable duration of action is needed if frequent awakenings during the night are the main feature of the insomnia and flurazepam and nitrazepam have been used for many years in this context. Low doses of these drugs should be used, but, even if residual effects on performance are avoided accumulation will occur with repeated ingestion. Sustaining sleep without residual effects and without accumulation on nightly ingestion is more likely to be achieved with the newer generation of rapidly (as opposed to ultra-rapidly) eliminated hypnotics, such as brotizolam and zopiclone, because their rates of elimination are still sufficiently fast for an appropriate dose to be free of residual sequelae.

It would appear that sustaining sleep without residual effects the next day with drugs in which the elimination phase is predominant demands a pharmacokinetic profile with a mean elimination half life of around 5 hours. Ultra-rapidly eliminated hypnotics with mean elimination half-lives between 2 and 3 hours (midazolam and triazolam) and hypnotics with a marked distribution phase are more appropriate when the only difficulty is falling asleep. With these drugs doses higher than those required to initiate sleep are needed to sustain sleep. Such high doses should be avoided as they may lead to high plasma concentrations during the early part of the night which could be accompanied by respiratory depression, alteration of sleep architecture, residual effects including anterograde amnesia, and rebound insomnia on cessation of continued therapy.

However, there is no convincing evidence that the benzodiazepines used as hypnotics have unavoidable adverse effects. Unnecessarily high doses for unnecessarily long periods are the main causes, and essentially adverse effects imply misuse. They include impaired performance the next day and anterograde amnesia, and such sequelae are of course of considerable significance in certain occupations. A variety of tasks have been used to investigate residual sequelae, and there is now broad agreement on the nature and persistence of impaired performance the next day with the various hypnotics available. Impaired performance the next day is largely related to dose and pharmacokinetic profile, and so the correct dose of the appropriate drug is essential.

Insomnia on cessation of treatment may also be a sequel to the misuse of hypnotics as rebound phenomena are a feature of many drugs if they are withdrawn suddenly. With rapidly eliminated hypnotics insomnia tends to occur during the first night or so after withdrawal, but with slowly eliminated drugs the fall in plasma concentration after withdrawal is unlikely to occur. Rebound insomnia occurs when relatively high doses of rapidly eliminated drugs are prescribed and especially when they are used nightly for several weeks. It is not observed when these drugs are used in appropriate doses for a limited period.

Dependency is also a possibility with the use of hypnotics. The possibility can be minimised by the intermittent use of low doses together with limited duration of ingestion, and gradual withdrawal in the event that continuous treatment has been given for more than a month. Dependency is less likely to present as a problem with hypnotics if they are used judiciously.

STIMULANTS

The potential role of stimulants in military operations is much more difficult. However, it is useful to review the pharmacological basis of the drugs which may help. There are three main groups of drugs which can be considered in this situation. Serotonin uptake inhibitors are important as seratonin is involved in the genesis of sleep. An uptake inhibitor will lead to wakefulness presumably because inhibition of uptake increases the amount of the transmitter in the synaptic cleft and pre-synaptic inhibition leads to cessation of release of the transmitter. This in itself leads to acute wakefulness. Dopamimetic drugs, of which amphetamine is an example discourage the uptake of the transmitter, encourage the release of the transmitter or have a direct stimulatory effect on the postsynaptic receptor. These mechanisms will all increase alertness. The third are the adenosine receptor antagonists, of which caffeine is an example. Their mechanism is not clear but the effect of adenosine on the postsynaptic receptor may well lead to sleep and this could be blocked by a drug such as caffeine.

How then can the usefulness of these drugs to sustain vigilance in complex patterns of work and rest be investigated? There are several techniques. We can ascertain whether the drug leads to wakefulness overnight. For instance, overnight sleep with pemoline (a dopamine agonist) shows dramatic increases in wakefulness and prolonged wakefulness. Performance overnight may be improved with caffeine, and this would be likely to suggest increased vigilance. Daytime alertness may be increased with an uptake inhibitor such as fluoxetine, and this would suggest improved vigilance. Essentially then, there is a variety of drugs with different mechanisms which increase alertness under different circumstances, but we need to know more about stimulants before we can use them effectively to sustain air operations, though of course we have to remember that caffeine is a widely used stimulant at the moment.

CONCLUSIONS

Maintaining the effectiveness of aircrew during intensive and sustained operations requires knowledge from many disciplines. The first is that of understanding how the performance of individuals is modified by unusual patterns of work and rest, and how deterioration in performance can be limited by the use of short periods of sleep. The

second is a detailed understanding of drugs and how they can be used either to preserve sleep or to maintain vigilance. The initial approach, if this is possible, must be to optimise the work pattern, but always we can optimise the pattern of rest. The most effective approach at present is likely to be the use of short periods of sleep, probably before rather than during duty periods, and to ensure restful sleep between operations by the use of hypnotics. At present the role of hypnotics is much less certain. Caffeine is used widely and is clearly effective, but drugs which modify monoaminergic transmission require a much greater understanding than we have today, both of their pharmacological effects on the central nervous system and their effects on performance, both advantageous and adverse, before we can consider using them in operations.

APPENDIX

HUMAN FACTORS AND AIR OPERATIONS IN THE SOUTH ATLANTIC CAMPAIGN

The operation during 1982 to regain sovereignty of the Falkland Islands involved air operations from an early stage, and it was anticipated that they would be difficult because of the distance of over 7000 miles from the United Kingdom to the Falklands, and the absence of forward airfields. Apart from aircraft which could operate from ships, the only other option was to use Ascension Island, which is almost exactly midway between the United Kingdom and the Falklands. Flights to Ascension were accomplished very easily, but the support of the task force from Ascension required return flights of up to 6800 miles. This posed problems for the aircrew, in particular disturbances of sleep inevitable in maintaining a continuous long-range air operation.

From the earliest phase the medical staffs at the Headquarters of Royal Air Force Strike Command and at the Royal Air Force Institute of Aviation Medicine were involved with advice on human factors for the aircrew and ground personnel. This included considerations of the crew task in flight, duration and frequency of flights, unusual patterns of work and rest, and rest facilities. The operation posed two problems: flights of very long duration and intensive rates of work.

Previous studies carried out during the early 1970s on reinforcing the Far East from the United Kingdom had involved several exercises with transport aircraft, and these suggested that, with some augmentation of the crew, the duration of individual flights could be extended to 30 hours - possibly involving loss of sleep over two consecutive nights. However, there was less information available on how frequently such flights could be operated over several weeks, though previous studies on aircrew in both civil and military transport operations provided some idea of workloads which would preserve an acceptable sleep pattern and this guideline was used initially.

However, it was evident at an early stage that the duty hours indicated by the guideline as being compatible with an acceptable sleep pattern would be far exceeded, particularly in maritime reconnaissance and in some transport roles, and that the operational requirement was most demanding. During the operation, flying rates were extended in many roles far beyond previous experience. This would have led to considerable sleep difficulties, and so from the early stages of the campaign hypnotics were used - particularly as the rest periods occurred at various times of the day and night, and because several weeks of disturbed sleep were envisaged.

The use of hypnotics in such a critical situation required a drug which was effective at any time of the day or night without a residual effect on awakening after 6 hours, and the facility to use the drug repeatedly at intervals of around 24 hours without the possibility of accumulation. This, in turn, required a hypnotic which was rapidly absorbed, and in which the plasma concentration fell below that of the minimum effective concentration for impaired performance before awakening.

Previous research at the Royal Air Force Institute of Aviation Medicine had shown that the 1,4-benzodiazepine, temazepam, a metabolite of diazepam which has no long-acting metabolite and which is rapidly eliminated, was a useful hypnotic for aircrew, and because of this experience - albeit in a less demanding situation - it was made available. Laboratory studies had raised the possibility that it may not maintain sleep under difficult circumstances but, in the event, it proved quite adequate.

Temazepam (Normison; Wyeth) was used widely. The majority of aircrew took 20 mg to get to sleep at various times of the day, and experienced good sleep without side or residual effects. They were advised to take the hypnotic at least 8 hours before flights and, whenever possible, were given an initial test dose to assess any untoward effect; none, however, was encountered. In many cases there was no time available to give the test dose, but such was the usefulness of the drug that crews found that they could fly 6 hours after taking temazepam without any ill effect. A brief account of the work of the crews - in particular those involved in maritime reconnaissance and long-haul transportation - will make this clear.

The maximum flying rate in peacetime for the Hercules transport crews is 120 hours per month, though this has seldom been achieved. During the South Atlantic Campaign it reached 150 hours per month, and this could involve six long-range flights with durations of up to 28 hours if a landing in the Falklands was not possible. Such flights usually extended over two nights. Most were achieved with augmented crews, which involved an extra pilot and navigator. Other crews were flying up to 19 hours in a single flight, and over a 3-month period some accumulated 360 flying hours. The very long flights were only possible with air-to-air refuelling: this was a new task, because the aircraft had never been used in this way before.

The problems associated with air-to-air refuelling from jet Victor tankers to turbo-prop Hercules were considerable and, because of speed differentials, a 'toboggan' descent for both aircraft was required during the refuelling procedure, resulting in a 10,000 ft loss of altitude. This had to be carried out twice on the southbound leg of a round trip, so that if the aircraft could not land in the Falklands it would be able to return to Ascension - 3500 miles away. Air-to-air refuelling was a major requirement in the campaign, and the Victor aircraft proved indispensable. The aircraft operated on a

daily basis out of Ascension. Up to 14 aircraft were required to position one aircraft in the total exclusion zone. The flights were of variable duration (2 - 14 hours), and involved flying hours up to 100 per month.

Nimrod crews were involved in intensive maritime reconnaisance, and some crews reached up to 100 flying hours in 2 weeks. Flights varied from 6 to about 20 hours, and the crews were augmented with one extra pilot and engineer. The aircraft spent many hours in transit and required air-to-air refuelling, which had previously not been attempted with this aircraft.

VC10 aircraft operated from UK to Ascension and were used throughout the campaign. The crews were not unduly stretched and did not require hypnotics, although their normal peacetime flying rates increased from about 20 to about 100 hours per month. The crews were on schedules similar to normal route flying, although flights were more frequent. VC10s were also used in the aeromedical evacuation role, and 11 flights from Montevideo conveyed 565 casualties to the United Kingdom.

Harriers (GR3) were rapidly equipped with refuelling probes, and the pilots were familiarized with aircraft carrier operations. The aircraft were flown to Ascension with inflight refuelling. This was a 9-hour flight accomplished without any major difficulty. Previous experience in the human factors of long-range, air-to-air refuelling had been gathered during such operations with Lightning and Phantom crews in the early 1970s.

Some Harriers were transferred to carrier operations and took over the offensive support role, leaving the Royal Navy to revert to air defence and fleet protection. Initially they operated from HMS Hermes, but after the landings 2 aircraft used San Carlos as a forward base. They operated during the day only, with the pilots normally flying twice a day and able to get adequate rest at night. During the campaign they flew over 150 support and low-level reconnaissance missions, losing 3 aircraft to enemy action. No pilots were killed, but one was taken prisoner.

Helicopters were in short supply and this was accentuated by the loss of 3 Chinooks on SS Atlantic Conveyor. The remaining Chinook flew intensively on the Falklands during the phase from the San Carlos landings to the recapture of Port Stanley, lifting most of the heavy equipment and about 80 troops at a time. Other helicopters involved in the campaign were Sea Kings, both in Ascension and latterly on the Falklands. All helicopter crews flew up to 10 hours per day, with a maximum of 120 hours per month compared with a peacetime maximum of 75 hours per month.

During the South Atlantic Campaign advice on human factors - particularly in relation to the problem of disturbed sleep - played an important part in maintaining air operations. Hypnotics were used extensively, and they ensured that adequate sleep was provided under difficult circumstances over many weeks.

Reprinted from Journal of the Royal Society of Medicine, Vol 76, November 1983, 933-937.

Discussion

Wurtman, US

. . (not recorded). . the serotonin uptake blocker because I've been working with the drug and several other similar drugs, symelidine and fluoramine to see if they could be used in treating certain types of obesity. And, in general, these compounds have as a side effect the production of sleepiness, which, of course, is quite the opposite of the effect you observed in the daytime. I think this can be explained by realizing that people's brains differ. If you give normal individuals a carbohydrate rich meal, this will also make some people very sleepy by increasing brain tryptohan and will have no effect at all in other people. I wonder, in your experience with fluoroxidine, have you ever observed significant variation from person to person. If that's the case, it would suggest that before using these drugs in an attempt to maintain vigilance, it would be important for each person to determine their particular pattern of response to the drug.

Nicholson, UK

In the 5-HT uptake inhibitors, as like yours, covered symelidine and also fluoroxidine, and they all have in common that they are predominantly uptake inhibitors of the serotonin. In terms of their selectivity this has always been a problem. We have studied these drugs in both nocturnal sleep and in daytime rest and in all the young adults we have examined wakefullness occurs with acute ingestion. As I explained, this is paradoxical. We would have thought that the 5-HT uptake inhibitors would lead to sleep and I know that in much clinical work it is stated that they are sedative. But I find this difficult to understand unless we're dealing with a chronic ingestion. In other words, with producing blood levels in which the presynaptic inhibition ceases to operate after a few days. But in acute use I think we're dealing with presynaptic inhibition.

Use of Tyrosine and Other Nutrients to Enhance and Sustain Performance

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Summary

Administration of supplemental tyrosine can increase the release of the catecholamines dopamine, norepinephrine, and epinephrine from physiologically-active neurons, and can thereby modify behaviors and other neuronal functions (e.g., control of blood pressure; neuroendocrine secretion) that are mediated by these neurotransmitters. The tyrosine acts by increasing the substrate-saturation of the enzyme tyrosine hydroxylase; when a given neuron is firing frequently this enzyme becomes phosphorylated and, consequently, tyrosine-dependent. The amount of tyrosine that enters the brain varies with the plasma tyrosine ratio, i.e., the ratio of the plasma tyrosine concentration to the summed concentrations of other large neutral amino acids that compete with tyrosine for transport across the blood-brain barrier. Hence, the administration of pure tyrosine is much more effective than eating proteins, which contain tyrosine: the proteins contain - and deliver to the blood stream - considerably larger amounts of the other large neutral amino acids. Tyrosine administration protects rats from the neurochemical and behavioral effects of stress; its ability to enhance performance of stressed humans is under exploration.

Our studies on the use of tyrosine and other nutrients to modify neurotransmitter synthesis and thereby affect behavior grew out of a research program started at MIT about a decade ago, dealing broadly with the effects of nutritional and metabolic factors on the brain and behavior. Initially, we showed that the rates at which the serotonin-releasing neurons in rat brain synthesize and release that neurotransmitter depend on brain levels of tryptophan (serotonin's amino acid precursor) [1,2,3]; thus serotonin-mediated neurotransmission was increased after animals received tryptophan, and could be increased or decreased after they consumed meals that modified the pattern of amino acids in the plasma. For example, if fasting rats were given a carbohydrate-rich, protein-poor meal, plasma levels of the large neutral amino acids (LNAA) other than tryptophan declined markedly because of the insulin secreted by the carbohydrate; as a consequence, the competition between these compounds and tryptophan for blood-brain barrier transport sites lessened, and more tryptophan entered the brain [4,5,6]. In contrast, consumption of a protein-rich meal selectively elevated plasma levels of the competing LNAA, thus diminishing brain tryptophan and slowing serotonin synthesis [5]. We subsequently affirmed that: a) food or tryptophan consumption causes the same plasma changes in humans as in rats [7] - and thus probably the same changes in brain serotonin; b) the effect of any tryptophan dose on the brain can be enhanced by giving it along with a carbohydrate, because of the resulting fall in blood LNAA; c) the increase in serotonin synthesis occurring when brain tryptophan levels rise is more-or-less independent of the firing frequency of the serotoninergic neurons [3]; and, d) food-induced changes in brain serotonin synthesis are associated with changes in physiological and behavioral functions thought to involve this transmitter (like pain sensitivity; sleepiness; appetite for carbohydrates; blood pressure; and the secretion of certain pituitary hormones [3,8,9]).

Subsequently, we observed that the syntheses of other neurotransmitters could also be affected by changing brain levels of their precursors: Giving choline (or oral lecithin, which dissociates to choline) could, under appropriate conditions, enhance acetylcholine synthesis [10,11] and release [12,13,14], while tyrosine administration could similarly affect the production of catecholamines, both in the brain [15,16] and in sympathoadrenal cells [17]. However, whereas tryptophan administration in physiologic doses (i.e., doses that kept plasma and brain tryptophan within their normal ranges) always accelerated serotonin synthesis, giving choline or tyrosine affected acetylcholine or catecholamine synthesis only when particular neurons happened to be firing frequently (that is, only when these neurons were physiologically active) [3]. This coupling has important physiological consequences: it apparently allows the brain to "choose" which particular catecholaminergic neurons will be "allowed" to respond - when subjects receive tyrosine or choline, or when they consume a meal that raises brain levels of these nutrients: If the quantity of catecholamine or acetylcholine being released from a particular set of neurons is sufficient for the brain's purposes, those neurons can, by slowing their rate of firing, protect themselves from changes in their outputs that would otherwise follow when plasma composition changes. A corollary of this relationship is that tyrosine or choline can, at least theoretically, be used to enhance neurotransmission, locally, in a disease state or when such transmission is inadequate for the body's needs (i.e., during prolonged stress or prolonged periods when focussed attention is required), without risk of severe side-effects. Of course, this corollary requires confirmation by experimental testing in each situation in which the precursor is proposed for use.

Some of the evidence supporting the conclusion that tyrosine-responsiveness is coupled to neuronal firing frequency follows:

1. Giving rats doses of tyrosine sufficient to double brain tyrosine levels failed to enhance the release of dopamine from nigro-striatal neurons (as assessed by measuring striatal levels of the dopamine metabolites DOPAC and HVA) in control animals, but caused major increases in dopamine release when animals were pretreated with:

a) haloperidol, a drug that blocks dopamine receptors, impairing synaptic transmission and thus accelerating nigro-striatal firing [16];

b) reserpine which depletes neuronal dopamine, thereby also impairing neurotransmission and secondarily accelerating nigro-striatal firing [18];

c) gamma-butyrolactone - which suppresses nigro-striatal firing, blocking the release of dopamine into synapses, thus blocking the activation of presynaptic dopamine receptors which normally diminish dopamine release [18]. (Like the above treatments, this drug activates the enzyme - tyrosine hydroxylase - that controls dopamine synthesis.)

d) chemical lesions destroying 75% or more of the neurons [19]. This treatment causes the surviving neurons to fire more frequently, thereby becoming tyrosine-responsive.

2. Tyrosine administration increases dopamine release from retinal amacrine cells when these cells are activated by exposing animals to light but not among rats kept in darkness -- even though retinal tyrosine cells rise by at least as much [19a].

3. Giving rats (or people) tyrosine can either raise blood pressure [20], lower it [21], or fail to affect it at all - depending on what the blood pressure happens to be at the time the tyrosine is administered (and which catecholaminergic neurons happen to be firing.) In hypertensive rats, the brain - in an effort to diminish blood pressure - activates norepinephrine-releasing neurons in the brain stem, causing, "downstream," a reduction in sympatho-adrenal firing. Hence, the brain stem neurons are responsive to tyrosine (because they are firing frequently); its administration causes them to make and release more norepinephrine (manifest as an increase in the levels of norepinephrine's metabolite MHPG-sulfate within the brain stem), thereby lowering blood pressure (18). In contrast, in hypotensive rats (made hypotensive by hemorrhagic shock), brain stem noradrenergic neurons are relatively inactive, and the sympathoadrenal neurons very active; now it is the latter neurons that respond to the tyrosine, making more norepinephrine and epinephrine, and raising blood pressure back to normal (20). It seems very useful that the system shuts itself off, as it were, terminating its response to tyrosine when blood pressure has returned to the desired range. (As described below, we have obtained additional evidence that tyrosine's ability to raise blood pressure in animals suffering from hemorrhagic shock results from an increase in peripheral, sympathoadrenal catecholamine synthesis: tyrosine's action in such animals is blocked by i) adrenalectomy; ii) pretreatment with carbidopa - which blocks amino acid decarboxylation in peripheral tissues but not in the brain -; and iii) pretreatment with phentolamine, a drug that blocks peripheral but not CNS alpha receptors. The anti-shock action of tyrosine is unrelated to the formation of tyramine [21A].)

Abundant additional evidence exists for the relationship between neuronal firing frequency and tyrosine-responsiveness, and tyrosine is currently being examined for possible use in such "catecholamine-deficiency" diseases as Parkinson's disease [22] and depression [23]. To our knowledge, every publication that has tested this relationship has confirmed it [e.g., 3,24,25].

At first we believed that the most probable mechanism that caused frequently-firing catecholaminergic neurons to become tyrosine-responsive had to do with the kinetics of the enzyme tyrosine hydroxylase. This enzyme does become activated when neurons containing it fire: One, two, or three of its amino acid residues become phosphorylated, changing its allosteric structure and very markedly enhancing its affinity for its tetrahydrobiopterin cofactor [26]. In its basal state, the enzyme is very poorly saturated with the cofactor, so that cofactor levels limit its overall activity. (It is also subject to considerable end-product inhibition by various catechols - which act to limit cofactor saturation.) Once phosphorylated, the enzyme becomes much more saturated with cofactor, and thus much more influenced by its relative unsaturation with tyrosine, - whose levels in brain are on the same order as the enzyme's Km, a range in which the enzyme would be expected to be most sensitive to small changes in tyrosine levels. The phosphorylation is reversible: When the neuron slows its firing, the enzyme becomes dephosphorylated, once again becoming limited by cofactor saturation [27]. However, we now have evidence that an additional mechanism, the depletion of tyrosine within catecholaminergic nerve terminals, may be just as important in allowing tyrosine administration to enhance catecholamine release [27a]. Tyrosine administration may "protect" against the reduction in transmitter release (from catecholaminergic neurons) that would otherwise occur with continuous firing, by keeping intraneuronal tyrosine levels from falling.

Tyrosine is a naturally-occurring amino acid. While it is possible to induce tyrosine toxicity experimentally (by giving animals massive tyrosine doses, and concurrently depriving them of adequate protein) [28], available evidence indicates that small, supplemental tyrosine doses are readily tolerated without side-effects by humans. If this tyrosine can amplify catecholamine release when such an amplification is desirable - for example, to sustain performance and the ability to cope when the locus coeruleus has been depleted of its norepinephrine in prolonged stress situations - it may have considerable utility. Some of the studies proposed below will examine the effects of various tyrosine doses on normal volunteers.

Rigorous testing of the possibly-beneficial effects of tyrosine on human performance is in its infancy; a description of published studies relating to these effects is provided in another paper presented at this symposium. It might be anticipated - on the basis of the animal studies described above - that tyrosine would do very little in normal people exposed to normal (i.e., non-stressful) environments, but might be quite effective in helping people sustain optimal performance when they are subjected to major and continuing demands. Future testing should tell.

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Discussion

Vogt, GE

What would you recommend for a pilot that has to work for 28 or 32 hours continuous operations?

Wurtman, US

My comments are not on pilots in similar circumstances but on people who were put under stress and in that circumstance I believe that subjects received 100 mg/kg. Now, the reason for using that dose is simply that everyone has always used that dose. That was the dose that was used on rats, 100mgm/kg, and so that dose was used on people. By the way, it does double the ration of plasma tyrosine to the competitors. The point is, we don't know where we are on the dose/response curve. It may be that lower doses will be equally effective or it may be that much higher doses would be far more effective. And I think it is important that dose/response studies be done. Also, it is terribly important to know what else the person is eating. If you give the tyrosine along with a piece of meat you will have so much leucine, isoleucine and valine it will block the uptake of tyrosine into the brain. On the other hand, if you give it with carbohydrate, starch or sugar, it doesn't matter, you will potentiate the effect on the brain. The important thing is to standardize in your experiments what the person is digesting when you give them the tyrosine. Well, again Dr. Banderet will be talking about their data and I believe those were single dose studies. If you are going to do studies of this sort, it is a very good idea to make a collaboration with a biochemist, perhaps you are one yourself, so that you can monitor, in a few subjects, the plasma tyrosine levels and the plasma tyrosine ratios. If you give the kind of dose they gave this will elevate the ratio for four or five hours and that's an adequate window for their experiments. But the field is in its infancy and I think such questions as dose and duration, I am sure will be worked out, but really must be worked out.

Von Restorff, GE

What was the dose of tyrosine you used and how often did you give that dose daily?

Banderet, US

In the recent study done by Banderet, Lieberman, et.al. it was a total dose of 100 mg/kg given in two divided doses about 50 minutes apart. This total dose was given previously in rat studies; it worked so we used it. Tyrosine has also been given to depressed patients in larger doses. References are given in Banderet et.al. paper.

DEVELOPMENT OF A PARADIGM TO ASSESS NUTRITIVE AND BIOCHEMICAL SUBSTANCES IN HUMANS: A PRELIMINARY REPORT ON THE EFFECTS OF TYROSINE UPON ALTITUDE- AND COLD-INDUCED STRESS RESPONSES

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SUMMARY

Tyrosine, a large neutral amino acid found in food, is the precursor for the catecholamine neurotransmitters dopamine and norepinephrine. Recent experiments have shown the behavior of animals given tyrosine is less impaired after stressful treatments than that of animals given placebo. Various environmental stressors are known to deplete central catecholamine stores and tyrosine's positive behavioral effects in animals are associated with reversal of this neurochemical deficit. Therefore, we investigated whether tyrosine administration would reduce adverse behavioral and physiological effects in humans induced by two combined environmental stressors, hypoxia and cold.

Twenty-seven young male military volunteers were tested in a double-blind crossover design. They were tested once with placebo and once with tyrosine at a control condition (550 m + 22°C) and at two levels of multiple environmental stressors (4200 m + 15°C and 4700 m + 15°C). A divided dose of 100 mg/kg of tyrosine or placebo was given 15 min before ascent to altitude and 50 min later. Behavioral assessment (a battery of performance tests and symptom and mood questionnaires) was begun 85 min after the initial dose and testing continued at specified times for the next 3 3/4 hours. Performance tests evaluated simple and choice reaction time to visual stimuli, vigilance, and processing of symbolic, numerical, verbal, and spatial materials. Three mood scales, a symptom questionnaire, and a sleepiness scale were also used. Blood samples were taken just before the first dose of tyrosine was given and again 150 and 265 min later. The samples were analyzed for plasma tyrosine and cortisol concentrations.

Performance, symptoms, and mood were adversely affected by both levels of high altitude and cold. Tyrosine administration in this exploratory study appeared to minimize the adverse consequences of these stressors. Tyrosine enhanced performance (e.g. complex information processing, vigilance, and reaction time) and reduced subjective symptoms (coldness, muscle discomfort, and headache). Mood states (e.g. anxiety, tension, and clear thinking) were also improved. Tyrosine had more beneficial effects at progressively more stressful altitude and cold conditions. Further research is necessary to replicate and extend the findings from this exploratory study.

MILITARY RELEVANCE

Future military operations will present unprecedented challenges. Combat is likely to be intensive, quick-paced, and fought day and night. Dramatic sleep loss, altered work-rest cycles, uncertainty, and misinformation will also be commonplace. Troops are also likely to be rapidly deployed to environments very different from that to which they are acclimated.

Military planners, doctrine developers, and commanders formulate strategies to sustain performance under a variety of adverse conditions. Special equipment, clothing, training, team building, and doctrine are some measures initiated to meet the challenges of varied combat theaters. In this study tyrosine, an amino acid in animal protein foods, was evaluated for its possible beneficial effects in a stressful situation, i.e. altitude and cold challenge. Such studies may aid the soldier by demonstrating nutritional substances can enhance his capabilities in stressful situations.

INTRODUCTION

Studies in rodents have demonstrated that some adverse physiological and behavioral effects of acute stress can be ameliorated by tyrosine, administered either in an acute dose or in the diet (1-3). Tyrosine is a constituent amino acid of many protein foods and is the precursor of the catecholamine neurotransmitters dopamine and norepinephrine (4). When tyrosine is administered in sufficient quantities, it can increase brain catecholamine concentration and turnover (4). When catecholaminergic

neurons are highly active they release more neurotransmitters (dopamine or norepinephrine), and therefore more substrate (tyrosine) is required. Since norepinephrine-containing neurons of the locus coeruleus have been shown to modulate alertness, activity and anxiety levels, the behavioral deficits associated with acute stress have been attributed to the depletion of norepinephrine in these neurons (5,6).

Animals that are acutely stressed display a combination of behavioral, cardiovascular and neurochemical changes (7). Behaviorally, they respond less to their environment, explore less, and generally seem debilitated. Simultaneously, brain norepinephrine turnover increases substantially and norepinephrine stores may be depleted. Tyrosine, given either systemically just before the stressful situation or as a dietary supplement, protected treated animals from both the neurochemical and the behavioral changes associated with tail shock and cold swim stressors (1-3). Tyrosine also lowers blood pressure in spontaneously hypertensive rats, subjected to stressful experimental conditions (8).

To date, we are aware of only a few studies where tyrosine has been administered to normal human subjects, although it may reduce depression in certain subgroups of depressed patients (9). In studies with normal subjects (10-12) no adverse effects of tyrosine administered in doses as large as 150 mg/kg were noted. In fact, two of these studies (11,12) showed a small improvement in mood and responsiveness following acute tyrosine administration. However, subjects in these studies did not experience experimental stressors, and it is under stressful conditions that tyrosine would be expected to have its greatest effects on behavior.

This study evaluated the benefits of administering tyrosine to humans during exposure to altitude and cold stressors. Altitude with cold has been shown to produce measurable impairments in affect and performance, important prerequisites for demonstrating a tyrosine effect. Also, hypoxemic effects should be maximal soon after ascent to altitude since previous studies (e.g. 13) suggested that cognitive performance impairments occurred at a simulated altitude of 4500 m (15,000 ft) within 60 min.

METHOD

SUBJECTS

Twenty-seven fully-informed medical research volunteers from Fort Detrick, MD, and the Natick Research Development and Engineering Center (Natick, MA) were subjects. The duration of their military service varied from a few weeks to over 9 years. This was the first research study for some subjects; others had served in many. About two-thirds of the subjects had not experienced high altitude before and none had participated in a tyrosine experiment. All subjects were given physicals; no subjects had medical histories that would contraindicate altitude and cold exposure.

ASSESSMENT METRICS

Behavioral (See Table I) and biochemical indices were used to evaluate cognitive performance, arousal, mood, symptoms, and responses to stress. These measures were collected using various media: 1) paper and pencil, 2) computer cards for Q-sort task, 3) portable computers with electroluminescent displays (Grid Compass II, Model 1131), and 4) blood samples.

Cognitive Tasks. Cognitive performance was assessed with the Addition, Coding, Map Compass, Number Comparison, Pattern Recognition and Tower Tasks. Sample items for each task are shown in Fig. 1. The Map Compass and Tower Tasks were developed in our laboratory (14); whereas, the remaining tasks were developed in the Navy's Performance Evaluation Tests for Environmental Research (PETER) program (15,16). All tasks were generated on a computer and printed, off-line, on a laser copier. Each performance task had 15 alternate forms. All tasks were previously shown to be sensitive to high altitude and/or other stressors (13,17).

TYPE OF TEST	TEST/SCALE/QUESTIONNAIRE	MEDIUM
COGNITIVE	ADDITION	PAPER & PENCIL
	CODING	PAPER & PENCIL
	MAP COMPASS	PAPER & PENCIL
	NUMBER COMPARISON	PAPER & PENCIL
	PATTERN RECOGNITION	PAPER & PENCIL
	TOWER TASK	PAPER & PENCIL
REACTION TIME	SIMPLE VISUAL REACTION TIME	PORTABLE COMPUTER
	FOUR-CHOICE VISUAL REACTION TIME	PORTABLE COMPUTER
VIGILANCE	DUAL TASK INFORMATION PROCESSING	PORTABLE COMPUTER
SYMPTOMS	ENVIRONMENTAL SYMPTOMS QUESTIONNAIRE	PORTABLE COMPUTER
MOOD STATE	CLYDE MOOD SCALE	Q-SORT (COMPUTER CARDS)
	MULTIPLE AFFECT ADJECTIVE CHECK LIST	PAPER & PENCIL
	PROFILE OF MOOD STATES	PAPER & PENCIL
	STANFORD SLEEPINESS SCALE	PAPER & PENCIL

Table I. Performance, symptom, and mood scales used in the study.

These performance tasks require cognitive processes inherent in many real-world tasks. For example, Map Compass requires association of direction and degree relationships, conceptualization of changing spatial relationships, and the ability to calculate distance or new grid coordinates. The Coding task requires that subjects write unique symbols for different numbers from the legend at the top of the page. This task is similar to manual procedures for encoding sensitive military communications. Subjects performing the Number Comparison Task indicate if two numbers are the same or different, much like comparing part numbers, grid coordinates, or numbers on property inventories. Pattern Recognition requires choosing a pattern (histogram), from an array of eight patterns, that is identical to the sample pattern. This is like recognizing computer programming, electronic, or map symbols. Subjects evaluate spatial problems on Tower Task with a series of learned algorithms and choose an appropriate strategy (14). Subjects are evaluated on their decisions, i.e. Is the problem "possible"? Is the problem "optimal"?.

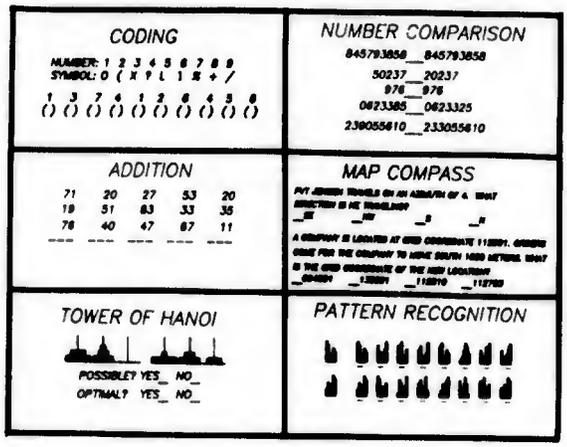

Figure 1. Sample items from the cognitive performance tasks.

The mental processes are like those for assembling mechanical components on a transmission or carburetor.

Reaction Time & Vigilance Tests. The Simple Visual Reaction Time (Simple RT), Four-Choice Visual Reaction Time (Choice RT), and Dual Task Information Processing Tasks (Dual-Task Vigilance) were administered on the Grid computers. After the presentation of a visual cue on the screen, the subject responds as quickly as possible in the Simple RT task. Such trials are repeated several times. Choice RT resembles the Wilkinson four-choice reaction time task and measures visual vigilance (18). On each trial a subject is presented a visual stimulus at one of four locations on the computer display. The subject strikes one of four adjacent keys on the keyboard to indicate the location of the stimulus.

Subjects simultaneously perform two tasks in the Dual-Task Vigilance test. One of the tasks is a modified version of the Bakan vigilance test (19); the other requires the "estimation of two classes of events in a signal stream". Our version of the Bakan test presents a series of three-digit numbers on the computer screen every 2.25 sec for 30 min. Each number usually differs from the previous number by one digit; however, occasionally all three digits are repeated. A subject's task is to detect such an occurrence. For the signal estimation test a single letter or digit is presented simultaneously on the display, to the right of the Bakan stimulus. Occasionally, the presentation of all stimuli is halted and subjects estimate the proportion of letters in the most recent series of stimuli. The proportion actually varies randomly from 0.2 to 0.8.

Symptom Questionnaire. Symptoms and subjective states were measured with the Environmental Symptoms Questionnaire (ESQ) as developed by Sampson (20). The ESQ was administered on the Grid Computer. It is a 67 statement questionnaire where each item is rated on a 6-point scale. Typical statements include: "I feel lightheaded", "I feel weak", and "I feel good". The ESQ factor structure is shown in Table II.

CLYDE MOOD SCALE (CMS)
FRIENDLINESS
AGGRESSIVENESS
CLEAR THINKING
SLEEPINESS
UNHAPPINESS
DIZZINESS
ENVIRONMENTAL SYMPTOMS QUESTIONNAIRE (ESQ)
CEREBRAL (ACUTE MOUNTAIN SICKNESS)
RESPIRATORY (ACUTE MOUNTAIN SICKNESS)
EAR, NOSE, AND THROAT
COLDNESS
DISTRESS
ALERTNESS
EXERTION
MUSCULAR DISCOMFORT
FATIGUE
MULTIPLE AFFECT ADJECTIVE CHECK LIST (MAACL)
ANXIETY
DEPRESSION
HOSTILITY
PROFILE OF MOOD STATES (POMS)
ANGER
CONFUSION
DEPRESSION
FATIGUE
TENSION
VIGOR
STANFORD SLEEPINESS SCALE (SSS)
SLEEPINESS

Table II. Subscales (factors) for the mood, symptom, and sleepiness questionnaires.

Mood Scales. The Clyde Mood Scale (CMS), Multiple Affect Adjective Check List (MAACL), the Profile of Mood States (POMS), and the Stanford Sleepiness Scale (SSS) were used to assess subjects' moods and arousal states. The factor structures for each of these scales are shown in Table II. The CMS consists of 48 adjectives, e.g. "good-natured", "troubled", "lonely", "impulsive", which are rated on a discrete anchor point scale ("not at all", "a little", "quite a bit", and "extremely"). The CMS was administered on computer cards as a Q-sort task for automated scoring (21). The MAACL has 132 adjectives such as "devoted", "healthy", "mild", and "panicky"; it is a paper and pencil mood scale (22). Subjects check those adjectives that apply to them. The POMS is also a paper and pencil scale; it has 65 adjectives (e.g. "bitter", "trusting", "lively") that are rated on a 5-point scale ranging from "Not At All" to "Extremely" (23). The POMS has been employed in many psychopharmacological studies and is sensitive to the effects of many different classes of psychoactive drugs, including hypnotics and stimulants. The Stanford Sleepiness Scale (SSS) consists of seven statements on a sleepiness-alertness continuum (24).

Biochemical Indices. Tyrosine was assayed after the methods of Shen and Abell (25) in 50 ul of plasma and using 200 ul of phenylalanine ammonia lyase (EC 4.3.1.5) in a total volume of 1.5 ml (0.1M Tris buffer, pH = 8.75) at 315 nm. Plasma cortisol levels were determined using radioimmunoassay test kits and techniques described in the technical bulletin (New England Nuclear Corporation, N. Billerica, MA). Normal values for adult male test subjects range from 4-24 ug.dl^{-1} using these techniques.

PROCEDURES

Experimental Design. Each group of subjects was tested over a 20 day interval. All training and testing sessions were in the altitude chamber at the U.S. Army Research Institute of Environmental Medicine, Natick, MA. The first week (Monday-Friday) subjects were trained and practiced on the various tests, scales, and questionnaires. On Friday subjects were also given a 50-min altitude orientation, e.g. shown how to open "ear (eustachian tube) blocks" during simulated altitude ascent or descent. This session also included an ascent to 4200 m for 15-20 min. Monday, Wednesday, and Friday of the second and third weeks were devoted to experimental testing. On a test day approximately half

of the subjects received tyrosine; the other half, placebo. The ordering of environmental conditions within a test week were roughly counterbalanced over the entire study. The environmental conditions for a group of subjects were identical on a given day, e.g. Wednesday, of both experimental weeks.

Subjects were tested in three groups (10, 5, and 12 subjects) in Jan., Feb., and late July 1986. Each group was always tested together, seated on metal chairs around two square tables. The schedule of activities, test sequence, time after initial ingestion of tyrosine, and time after ascent to altitude is shown in Table III. This schedule was the same for all groups. Subjects wore the Army's battle dress uniform to control clothing (heat loss) variables. The day before each test day subjects were told to refrain from alcohol; that evening they were housed in a special dormitory beginning at 2200 hours.

TIME (H)	ACTIVITY	MINUTES AFTER 1ST TREATMENT	MINUTES AFTER ASCENT	ASSESSMENT INSTRUMENTS
0535-0540	WAKE-UP CALL			
0540-0650	SHOWER & SHAVE			
0650-0650	SPECIAL BREAKFAST			
0650-0700	GO TO ALTITUDE CHAMBER			
0700-0715	BLOOD PRESSURE 1			
0715-0730	BLOOD & TREATMENT 1	0		
0730-0740	ASCENT TO ALTITUDE	15	0	
0740-0805	RELAXATION TIME 1	50	15	
0805-0820	TREATMENT 2	50	55	
0820-0840	BLOOD PRESSURE 2	70	55	
0840-0910	COGNITIVE TESTS	95	80	PR1,ADI,CDI,MCI,MCI, TWI
0910-0930	REACTION TIME & MOOD TESTS	120	105	CHOICE RT, PDMS1, SSS1
0930-0940	COGNITIVE TESTS	135	120	PR2, ADZ
0940-1005	BLOOD 2 & BREAK 1	150	135	
1005-1045	VIGILANCE & MOOD TESTS	185	170	PDMS2, SSS2, DUAL TASK
1045-1100	COGNITIVE TESTS	210	195	CD2, MC2, PC2
1100-1115	BLOOD PRESSURE 3 & BREAK 2	225	210	
1115-1120	MOOD TESTS	235	220	CRS1 & MAACL1
1120-1140	REACTION TIME & MOOD TESTS	250	235	PDMS3, SSS3, & SIMPLE RT
1140-1150	BLOOD 3 & BREAK 3	265	250	
1150-1205	SYMPTOM & COGNITIVE TESTS	275	260	ESQ1 & TW1
1205-1215	DESCENT FROM ALTITUDE	290	275	

Table III. Schedule of activities for an experimental test session.

Treatment. Tyrosine and placebo (cellulose) administration were double-blind. A total of 100 mg/kg of tyrosine was administered; this corresponds to about 80% of the daily dietary intake of tyrosine. Tyrosine or placebo was loosely packaged and administered in gelatin capsules (300 mg per capsule). The ordering of tyrosine or placebo for a subject was random for the first three treatment administrations with some restrictions. Ordering for the 4th, 5th, and 6th administrations was the opposite. Each subject received one-half of the total dose of tyrosine or placebo immediately before each test session. Approximately 50 min later each subject received the second divided dose. To minimize "first day" effects, all subjects ingested capsules (placebo) the fifth training session. Subjects were informed this was a test trial. For dietary control, subjects ate a light breakfast (apple or cranberry juice and two cereal bars) each morning soon after awakening. Decaffeinated coffee and water were also available.

Environmental Stressors. Environmental conditions on a test day were one of three conditions: 550 m + 22°C (1800 ft + 72°F), 4200 m + 15°C (13,800 ft + 59°F), or 4700 m + 15°C (15,500 ft + 59°F). The relative humidity was 30-50% and ventilation 0.71 cu m/min (25 cu ft/min). Environmental exposures were 280-290 min per day. Test subjects were not informed regarding the specific environmental conditions to be tested on a given day. During training ambient conditions were normobaric and thermoneutral (75 m + 22°C).

Cognitive Performance. All cognitive performance tasks were timed. Addition, Coding, Number Comparison, and Pattern Recognition were given for 3 min; Map Compass, for 4 min and Tower Task, for 6 min. Repeated testing procedures and methods were similar to those for the Performance Evaluation Tests for Environmental Research Program (13-16). Initially, subjects were given training and extensive practice with performance feedback. Feedback was no longer given after the 5th training day. All performance tasks were practiced repeatedly to insure performance was stable and near maximum. Each task had been completed 15 times before the subjects were evaluated in an experimental condition.

Reaction Time and Vigilance. After five warmup trials were given on Simple RT, 300 test trials were presented. Both errors of commission (responding before the visual stimulus is presented) and errors of omission (response latency >1 sec) were recorded. Five hundred Choice RT trials were administered in 10 min. Response latency and errors of omission and commission were recorded.

Subjects pressed a key on the Dual Task Vigilance Task when they detected a three-digit number on the display the same as the number just preceeding it. In addition, at six intervals (each 200 trials) the presentation of all stimuli was halted and subjects estimated the proportion of letters in the last series of 200 stimuli.

Mood and Symptoms. All mood and symptom scales were untimed. Subjects were instructed to "describe how you feel NOW" on each mood and symptom scale.

Biochemical Indices. A blood sample (< 20 ml) was taken from an antecubital arm vein of each subject using heparinized vacutainers just before ingestion of the first dose of tyrosine or placebo. A second and a third blood sample was withdrawn approximately 150 and 265 min later. Blood samples remained on ice during a sampling interval until aliquots from all test subjects were obtained. Samples were then centrifuged (4°C, 1500 g), the plasma separated, and aliquots prepared and frozen (-20°C) for subsequent assay. Tyrosine and cortisol were assayed.

Statistical Analyses. Separate analyses of each environmental condition compared the tyrosine and placebo outcomes (t-test, repeated measures). This strategy was chosen over an analysis of variance (across altitude conditions) because it allowed use of the maximum number of subjects in each analysis. Missing values occurred in the data base because approximately one-third of the subjects did not complete at least one test session due to ear infections, blocked sinuses, or other illnesses. Results are presented for all measures that detected statistically significant differences between tyrosine and placebo ($p \leq .05$) as well as tests that showed differences ($p \leq .15$). All comparisons are one-tailed.

A measure of cognitive performance was derived to reflect the combined effect of rate and accuracy changes, i.e. number of problems correct/min = (number of problems attempted - number of problems wrong)/min. In calculating this index a 2X weighting factor was applied to errors for Number Comparison and Tower Task to penalize for possible guessing on dichotomous responses. Corresponding weighting factors were applied to the Map Compass and Pattern Recognition tasks which have more than two response

alternatives.

Average reaction times for each subject were analyzed on the Simple RT and Choice RT tasks. Number of errors of commission was also analyzed on the Choice RT task. The number of critical stimuli correctly detected by each subject was analyzed on the Dual-Task Vigilance Task.

Unnormalized factor or raw scores were analyzed on the mood and symptom questionnaires.

RESULTS

Shown in Fig. 2 are plasma levels of tyrosine for each environmental condition for the initial subjects from groups 1 and 2. Values for subjects receiving tyrosine and subjects receiving placebo are shown before capsule ingestion and 150 and 265 min after

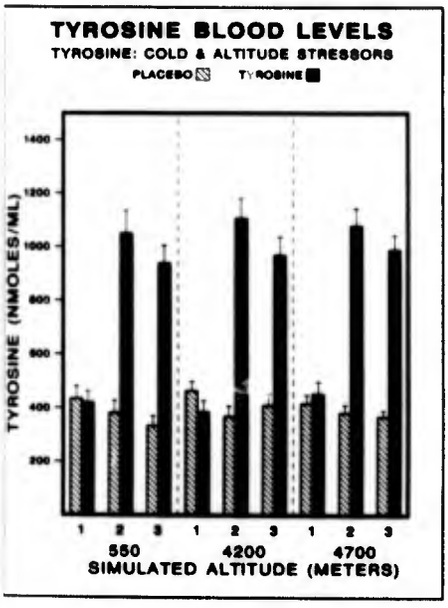

Figure 2. Circulating plasma tyrosine levels after tyrosine or placebo ingestion . Values for tyrosine- and placebo-treated subjects are shown for three levels of multiple environmental stressors (550 m + 22 °C, 4200 m + 15 °C, and 4700 m + 15 °C) and for three sampling intervals (before capsule ingestion, and 150 and 265 min later). The standard error of the mean is also indicated.

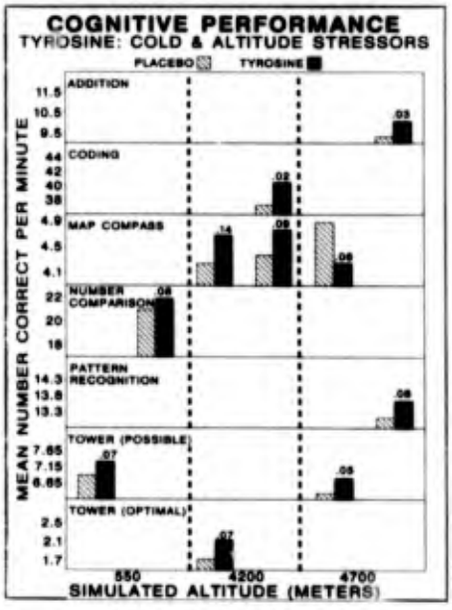

Figure 3. Performance on several cognitive tasks after tyrosine or placebo ingestion for three levels of multiple environmental stressors (550 m + 22 °C, 4200 m + 15 °C, and 4700 m + 15 °C). Actual probabilities for all treatment effects ($p \leq .15$) are shown. Tyrosine enhanced cognitive performance, except for Map Compass at 4700 m + 15 °C.

ingestion. These data indicate that after tyrosine ingestion a significant ($p \leq .001$) elevation in circulating tyrosine occurred in both subsequent blood samples; however, these increments were unaffected by either combination of altitude and cold. Tyrosine levels were highest in the second blood sample, taken approximately 150 min after tyrosine ingestion, and then fell slightly 265 min after tyrosine ingestion.

Preliminary data for circulating cortisol levels at sea level indicated there was a significant ($p \leq .05$) decrement in cortisol concentrations from the first to the third blood sample, irrespective of tyrosine ingestion. This decrement is consistent with the anticipated circadian reduction which ordinarily occurs between approximately 0700-1100h (26). Interestingly, for both altitude conditions, the trend toward decreasing cortisol levels is apparent, but the lowest levels attained, especially at the third sampling time, are not as depressed as in the sea level session. However, examination of the data for the 4700 m altitude (and cold) condition, at which physiological stress might be expected to be maximal, indicates no effects of tyrosine on cortisol levels; in fact, in both the second and third blood samples, cortisol levels in tyrosine-treated subjects are slightly elevated.

Fig. 3 shows the results from the cognitive performance tasks. Plotted values represent average performance levels at 550 m + 22 °C, 4200 m + 15 °C, and 4700 m + 15 °C that were different ($p \leq .15$) for the tyrosine- and placebo-treated subjects ; the exact probability for each comparison is shown above the solid bar (tyrosine). There were two

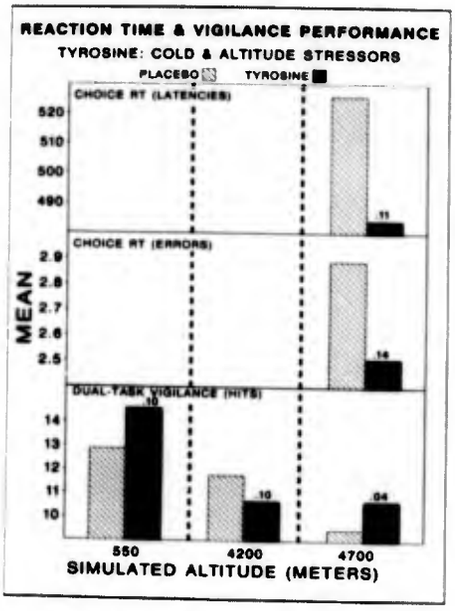

Figure 4. Reaction time and vigilance performance after tyrosine or placebo ingestion for three levels of multiple environmental stressors (550 m + 22 °C, 4200 m + 15 °C, and 4700 m + 15 °C). Actual probabilities for all treatment effects ($p \leq .15$) are shown. Performance was enhanced by tyrosine, except for Dual Task Vigilance at 4200 m + 15 °C.

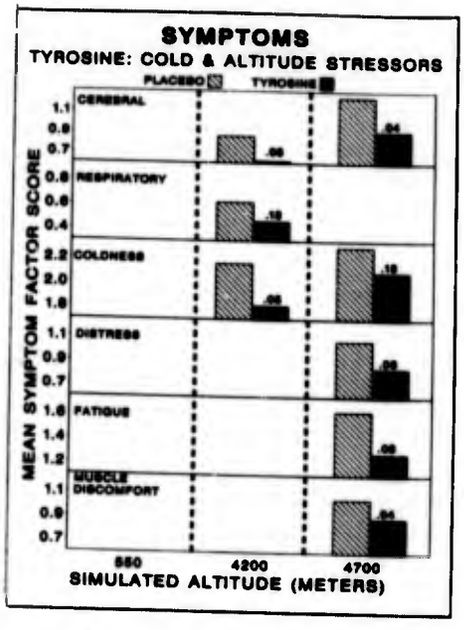

Figure 5. Self-rated symptoms after tyrosine or placebo ingestion. Actual probabilities for all treatment effects ($p \leq .15$) are shown. Tyrosine consistently reduced symptoms associated with the combination of environmental stressors (simulated high altitude and cold).

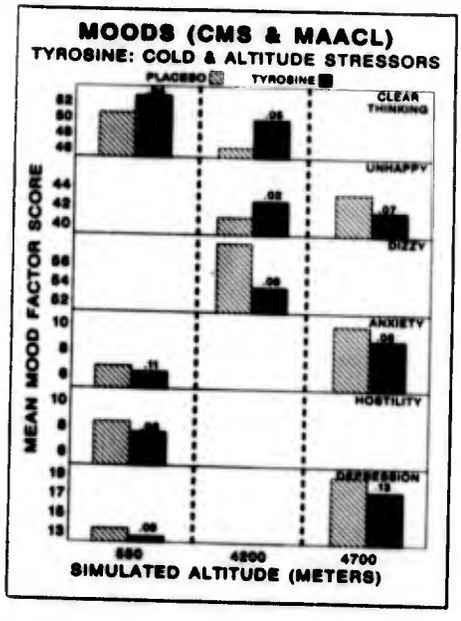

Figure 6. Self-rated mood states as measured by the Clyde Mood Scale (top three factors) and the Multiple Affect Adjective Check List (bottom three factors) after tyrosine or placebo ingestion. Actual probabilities for all treatment effects ($p \leq .15$) are shown. Tyrosine improved moods affected by the high altitude and cold conditions and the control environmental condition, except for the unhappiness factor at 4200 m + 15 °C.

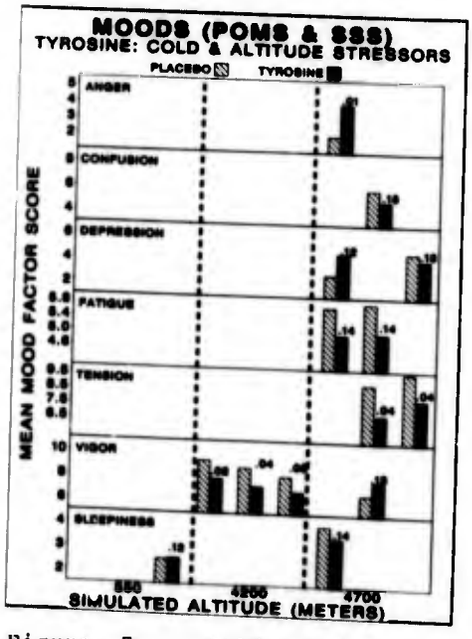

Figure 7. Self-rated mood states as measured by the Profile of Mood States (upper six factors) and Stanford Sleepiness Scale (lower factor) after the tyrosine or placebo ingestion. Actual probabilities for all treatment effects ($p \leq .15$) are shown.

MEASURE	550 m + 22°C p≤.05	p≤.15	4200 m + 15°C p≤.05	p≤.15	4700 m + 15°C p≤.05	p≤.15
COGNITIVE PERFORMANCE	0	2	1	4	2	4 (1)
REACTION TIME/VIGILANCE	0	1	0	1 (1)	1	3
SYMPTOMS (ESQ)	0	0	1	3	2	5
MOOD STATE (CMS & MAACL)	1	4	2 (1)	3 (1)	1	3
MOOD STATE (POMS & SSS)	0	1 (1)	2 (2)	3 (3)	3 (1)	10 (2)
TOTALS	1	8 (1)	6 (3)	14 (5)	9 (1)	25 (3)

Table IV. Performance, symptom, and mood treatment comparisons for tyrosine- and placebo-treated subjects. The number of statistically significant effects ($p \leq .05$), number of differences ($p \leq .15$), and instances when placebo was superior to tyrosine are shown; all comparisons were one-tailed. This analysis suggests the treatment effects are subtle in this exploratory study and may be hidden by measurement variability in our subject population.

test administrations per day, e.g. Map Compass showed a difference with 4200 m + 15°C for both the first and second test administrations. Enhanced performance is reflected in more problems correct/min. With the exception of the Map Compass data for 4700 m + 15°C (1st admin.) all treatment effects were in the expected direction. Beneficial tyrosine effects were demonstrated on all cognitive performance tasks for at least one environmental condition. Statistically significant ($p \leq .05$) treatment effects were seen on the coding task at 4200 m + 15°C and on the Addition and Tower Task (possible) at 4700 m + 15°C.

Fig. 4 shows the reaction time and vigilance performance measures. No evidence of treatment effects were observed for Simple RT. Reaction time and error measures on the Choice RT Task were decreased by tyrosine for the 4700 m + 15°C condition. Correct detections (i.e. hits) on the Dual-Task Vigilance Task increased with tyrosine at 550 m + 22°C and 4700 m + 15°C. Unexpectedly, Dual-Task Vigilance performance was impaired by tyrosine at 4200 m + 15°C. Increased Dual Task hits in tyrosine-treated subjects at 4700 m + 15°C were statistically significant ($p \leq .05$).

Fig. 5 shows the effects of tyrosine upon symptoms as measured by the ESQ. Tyrosine reduced symptom severity in every treatment-difference ($p \leq .15$). Cerebral discomfort, e.g. headache, and coldness were reduced by tyrosine at both 4200 m + 15°C and 4700 m + 15°C. Respiratory discomfort was also less at 4200 m + 15°C in soldiers given tyrosine. Distress, fatigue, and muscle discomfort at 4700 m + 15°C were also less in tyrosine-treated subjects. Statistically significant effects ($p \leq .05$) were seen for the cerebral and muscle discomfort factors at 4700 m + 15°C and for the coldness factor at 4200 m + 15°C. No tyrosine effects were found at sea level with this symptom questionnaire nor were there any treatment effects on the alertness, exertion, or ear-nose-throat factors (See Table II).

Fig. 6 shows tyrosine treatment effects as measured by the CMS (upper three factors) and the MAACL (lower three factors). Clear thinking was improved by tyrosine at 550 m + 22°C and 4200 m + 15°C, and the dizziness factor was improved at 4200 m + 15°C. Unhappiness factor scores were improved at 4700 m + 15°C by tyrosine but made worse at 4200 m + 15°C. The friendliness, aggressiveness, and sleepiness factors on the CMS did not exhibit any treatment effects.

Treatment effects were found with the MAACL at both 550 m + 22°C and 4700 m + 15°C; no mood factors were improved or made worse at 4200 m + 15°C (see lower part Fig. 6). Anxiety, hostility, and depression were reduced at 550 m + 22°C; anxiety and depression were also reduced at 4700 m + 15°C. Statistically significant beneficial effects ($p \leq .05$) were seen on the clear thinking scale (CMS) at 550 m + 22°C and 4200 m + 15°C and the anxiety scale (MAACL) at 4700 m + 15°C. Changes in unhappiness at 4200 m + 15°C were in the wrong direction ($p \leq .05$).

The POMS and SSS data are shown in Fig. 7. The first six factors, anger thru vigor, are for the POMS; sleepiness is for the SSS. Data are shown for three administrations of each scale at each environmental condition. Consistent with the other mood questionnaires, confusion, depression, fatigue, tension, and sleepiness were decreased and vigor was increased by tyrosine for the 4700 m + 15°C stressor condition on one or more administrations. A statistically significant ($p \leq .05$) beneficial effect was seen at 4700 m + 15°C on the tension scale. For unknown reasons some mood factors on the POMS detected changes inconsistent with the direction of our performance, mood, and symptom data above. Unexpectedly, depression and anger increased in tyrosine-treated subjects during the first administration of the 4700 m + 15°C environmental condition. Also, vigor was always decreased during the 4200 m + 15°C condition and sleepiness was increased at 550 m + 22°C.

Table IV summarizes the behavioral data by showing the number of times the treatment effects, i.e. placebo and tyrosine comparisons were different ($p \leq .05$ and $p \leq .15$) for each of the environmental stressor conditions. Unexpected instances of treatment-produced impairments are shown in parentheses. Increasing levels of environmental stressors resulted in more treatment effects, e.g. 1, 6, and 9 ($p \leq .05$) or 8, 14, and 25 ($p \leq .15$). Secondly, conventional significance levels, e.g. $p \leq .05$, resulted in 16 significant differences with four in the opposite direction from that expected for a beneficial tyrosine effect. The likelihood of 12 effects out of 16 (in the expected direction) being due to chance is less than 5 in 100. Examining data from the less stringent statistical level in the same manner yielded 47 treatment effects with 38 in the expected direction. The chances of this outcome being due to chance are less than 3 in 100,000.

DISCUSSION

To the best of our knowledge this exploratory study represents the first systematic attempt to determine if tyrosine has beneficial effects on humans exposed to stressful situations. The overall results tentatively suggest that tyrosine may improve certain aspects of performance and mood states under conditions of acute stress produced by simulated high altitude (hypobaric) and cold. Tyrosine's beneficial effects on performance were detected by several cognitive tests and tests of choice reaction time and vigilance. Tyrosine also reduced symptoms associated with acute exposure to hypoxia and cold stress such as fatigue, distress, and cerebral discomfort. Appropriate changes in mood state after tyrosine administration were also noted. For example, clear thinking was increased and dizziness and tension were decreased. Results obtained under the control environmental conditions suggest that tyrosine administration may have positive effects when minimal stress is present. Although potentially adverse effects of tyrosine on some mood states were observed on one of the three mood scales, i.e. the POMS, tyrosine generally produced improvements in performance, symptoms, and other mood states. The majority of mood changes detected (17 of 24, $p \leq .15$) were in the expected direction. Such improvements in mood were consistent with the beneficial effects of tyrosine on performance and symptoms concurrently observed. The occasional adverse effects on mood state that were noted on the POMS are difficult to explain since unlike the positive treatment effects detected, their pattern was not consistent across altitude conditions or other mood questionnaires.

The effects of tyrosine were greatest under the most adverse environmental conditions employed in this study, the simulated 4700 m and 15°C condition. For this condition, 22 treatment comparisons showed beneficial tyrosine effects ($p \leq .15$), i.e. reduced symptoms and improved performance and mood. Nine statistically significant improvements ($p < .05$) in performance and mood were observed at this altitude. Only one statistically significant adverse finding (anger factor on POMS) was noted.

Overall, the tyrosine effects observed were selective for the various behavioral parameters assessed, i.e. no effects on some mood factors (e.g. friendliness and aggressiveness) and performance tests (Simple RT). Treatment effects also appeared modest in magnitude. This is consistent with other studies which indicate that neurotransmitter precursors will produce more selective effects on behavior than drugs with similar properties (12,26). Actually, even high doses of psychoactive drugs rarely produce effects on all parameters assessed. Rather, effects are typically seen on a very limited number of dependent variables measured. This is probably the result of considerable differences in sensitivity across measurement instruments, as well as differences in the nature of the underlying parameters measured. It is particularly difficult to detect acute, effects of anti-anxiety agents. Consequently, in acute psychopharmacological studies with such drugs, relatively high doses must be administered and a large population sampled to detect reductions in anxiety (28). Additionally, the classic anti-anxiety agents, the benzodiazepines and meprobamate, typically impair task performance and reduce subjective alertness, although they do reduce self-reported anxiety (29). Based on our preliminary findings, tyrosine would appear to have a number of advantages compared to these drugs in some circumstances.

The relatively modest behavioral effects detected in this study may be the consequence of the relatively mild level of stress produced by our environmental conditions, the predictability of each daily test session, and the statistical power of our assessment instruments. Support for this is indicated by the smaller number of positive effects seen for the 4200 m + 15°C condition and by the modest changes in plasma cortisol produced by even the greatest altitude-cold condition. Preliminary calculations of statistical power suggest several of our tests would have marginal ability to detect treatment differences with the magnitude of the effects observed and our smaller number of subjects for some conditions (30). Also, it seems likely that some portion of the performance and mood impairments, observed for the combinations of hypoxia and cold, were attributable to reduced oxygen delivery to the brain or some other direct effect of altitude on central nervous system functioning. In fact, although cold stress has been reported to deplete catecholamine stores, hypoxia appears to have a relatively modest effect on central catecholamine function (7). Tyrosine would not be expected to reduce adverse effects directly attributable to central oxygen insufficiency. This may be critical since tyrosine would be most effective for alleviating the effects of an acute generalized stress response.

In general, this exploratory study indicates that tyrosine may be an appropriate intervention to enhance performance and mood states and decrease symptomatology in acutely stressful environments. While the beneficial effects of tyrosine we detected were limited, the adverse effects of other anti-anxiety agents on performance, such as the benzodiazepines, rule out their use in any situation where optimal task performance is required. Additionally, tyrosine may have fewer unwanted side effects since it is a nutrient that is present in substantial quantities in the diet.

Further research is necessary to determine optimal tyrosine doses, tyrosine's effects in other stressful situations, and the replicatibility of the preliminary findings from this exploratory study.

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ACKNOWLEDGEMENTS

In a multi-institutional and multi-disciplinary experiment, critical people contribute in many unique ways. We especially thank Ms. Gail Emde of MIT, Ms. Edith Crohn, SFC Adrien Lussier, SSG Calvin Witt, SGT Tony Marshall, SP4 Linda Palian, SSG Carrol Crawford, Ms. Donna Boucher, MAJ Bruce Jones MD, and MAJ William Hill MD. To others, too numerous to recognize individually, their professionalism and talents were critical for the successful completion of the study and the rapid preparation of the report. We think especially of the altitude chamber crew and staff, cognitive test scoring team, the phlebotomists and chemical assay team, Test Subject Support Group, and the laser copier and data entry groups (Information Management Directorate). Support for the MIT components of the study was provided by NASA grant NAG 2-210 and NIH grant 5R01-AG 04591.

Lastly, we cite the twenty seven subjects who volunteered for this experiment that required several blood samples, repeated exposures to harsh environments, and prolonged behavioral assessment. The results of this experiment attest to their commitment and dedication to duty.

ADDENDUM

The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers in Research.

Discussion

Nicholson, UK

Well, I'd like to compliment you on what must have been a very big study, indeed. But looking at the data, I'm afraid that I'm not very convinced of your interpretation. It looks to me that there is no effect at all of tyrosine and I'd like to ask just a few questions on the analyses that you've done. Having to use such very low levels of significance this does imply that you really had very highly variable data and I worked out that you must have done somewhere around 300 or 400 comparisons, 200 at least. Well, that's what I've worked out. And from that you would expect, in my calculations, at least 30 or 40 to come out at the 15% level merely by chance. I'd like you to comment on that. And the other point is that you said there were a lot of missing data here. Did you do an anlysis as to those who didn't complete the test for various reasons? Were they on tyrosine or were they on the placebo. But I think the thing that does worry me is, working at 15%. I think you worked at 15% significance levels which I work out at 30 to 40 of those would come out by chance in any case.

Banderet, US

OK, could we go back to the slides, please? Dr. Nicholson, let me comment first of all on the missing data. What was very characteristic in the study, and this is a function of investigating simulated high altitude, where you are going to be working with pressure differences, is that people are excluded from the study before it begins in the morning. In other words, a physician associated with the study looks at them and says this person has bad ears. We are not letting him go up into the chamber. So it is not a matter of being in one condition or the other , they never make it into the study. The second thing is in answer to your criticism, and I would add, I think you're partly on target, but I think you're extremely harsh. This is something we've looked at and looked at very carefully. First of all, there is something like 170 comparisons that are made and one of the points I would like to make is that in that particular table there were, that last questionnaire--the last two questionnaires--which was administered three times, the Stanford Sleepiness Scale and the POMS, they contributed a disproportionate number of reversals to that entire table because there are something like 65 comparisons resulting from those two questionnaires alone. So over 1/3 of all comparisons result from that. That is point number one. The other comment is that with that reduced number of comparisons we are still running above the chance level. It is not dramatically above, but it is above. And I think the question that we and other people would have to answer is, were we, in fact dealing with random chance, then why wouldn't we expect that our treatment reversals would be just as likely in one direction as the other. The fact that we can demonstrate, with very good odds, that these things are turning out in the direction that one would expect for the treatment effect, I think offers at least some compelling evidence for the fact that we are dealing with something, but it is fairly soft. I can see that it it soft, but I think it is real.

Moore-Ede, US

. . (not recorded).. work of the translation of hypothetical frameworking towards reality and application. It's an enormously challenging thing to do. The one thought that I had as I looked at this data was that it seemed the most consistent effects were observed in the subjectively reported symptoms, that is they all went in the same direction. This is a consistent finding. The one possibility that occurred to me was to wonder whether the subjects could detect whether they were taking a placebo or the tyrosine. In other words, do you have any sense that they in fact could have a pretty good guess at which it was after they had taken it?

Banderet, US

. . (not recorded). .and we have not yet had a chance to work those up. We finished the study the first week in August and I'll just offer what was an impression at the time. I mentioned that we investigated different environmental conditions and these were all sublimed in subjects and we were rather amazed at the subjects' inability to discriminate the difference between the 4200 meter and the 4700 meter condition. So, I don't know the answer to the tyrosine question, but let's say that if they were aware of it, there was certainly nothing dramatic that emerged as we ran the study. Again, we do have a questionnaire that we put together, where we actually asked them whether or not there were things that they were responding to but we have not had a chance to look at it.

Rostorff, GE

From the paper of Dr. Wurtman, I learned that tyrosine is only effective if the body really needs it. So my question is, in one of the first slides, you showed the tyrosine levels and the placebo medication. Was the decrease that was visible in some subjects under some conditions, statistically significant between control and your experimental conditions? That is, to put it in other words, did the body of your subjects need the tyrosine you gave them, and therefore was there a need for this tyrosine study?

Banderet, US

OK. I think that we can say that, I won't say that the body needed the tyrosine. But I think we can say from the data that I've shown you, that in fact there were some benefits that were accrued having taken it. One of the greater suprises to us, which I think speaks indirectly to your question, is the fact that we did end up with some of these treatment effects in the control environmental conditions as well as the more

moderate environmental conditions. And in thinking about how you account for that, I think it's another one of those situations where we define the stressor in terms of the environment. That's how we work--manipulating it--that's how we were looking at it. But sometimes we forget that there is a lot of stress that these test subjects bring into the study, be it from the girl back home, be it that they are fighting with the fellow over in the barracks, be it that they have some financial problems. And that's the most current explanation that we are using to account for some fo the beneficial effects, for example, that were observed during the control condition. Some of those real world, real life stresses that people bring to the study that may benefit from the tyrosine.

Price, US

Could you relate the treatment reversals at all with the sequencing of the tests? That is, you mention that you had a crossover design. I was wondering if the added burden of annoyance of having the more difficult stress towards the end created any difference as opposed to having it at the beginning.

Banderet, US

OK, I'm very glad that you mentioned that. First off, remember that the sequencing of the environmental effects was different for each of the groups, so that over the course of the entire study the environmental conditions were fairly randomized throughout the week. That doesn't change the fact, however, when you take a particular group, and you have some particular dynamics going on, the attention in the group is something else, that you start loading in some effects which are specific to the ordering or when these things happen. So, yes, we did look at that and in fact some of the reversals, not all, but I think that one can understand some of the reversals better from looking at them in terms of ordering effects and those kinds of factors. That's not an explanation, but I think it helps you modulate what you're looking at.

Von Restorff, GE

From the paper of Dr. Wurtman, I learned that tyrosine is effective only if it is needed by the body. Do your data in your control subjects indicate such a need for tyrosine by a statistically significant decrease in plasma level under placebo medication?

Banderet, US

We do not known what are minimum essential tyrosine levels. The fact that we observed treatment effects for our control conditions (550m + 22°C) and our moderate stress condition (4200m + 15°C) suggests indirectly that our subjects did benefit from higher circulation tyrosine levels, even under moderate and low stress conditions.
It is likely that subjects bring other stressors to the study, e.g. interpersonal difficulties, family difficulties, etc. This perhaps suggests why tyrosine was beneficial under our experimental control and our stress conditions.
Our biochemical assays for plasma tyrosine also suggest placebo-treated subjects do show slight decreasing tyrosine levels during our experimental sessions (inferential statistics were not calculated). This trend appears similar for placebo-treated subjects we studied and may represent a circadian effect or evidence of tyrosine utilization.

MULTIVARIATE AND PSYCHO-PHYSIOLOGICAL FUNCTIONS OF DSIP

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Summary

From 1969 to 1977 we isolated, characterized and synthesized the Delta-Sleep-Inducing-Peptide (=DSIP). DSIP beside humoral sleep induction acts upon the circadian rhythmicity of the locomotor activity and transmitter concentrations in the brain as well as on that of plasma proteins and cortisol levels in rats. It influences the prolactine levels and the circadian activity of N-Acetyl Transferase. DSIP-like immunoreactive material showed a circadian rhythmicity in breast milk during normal lactation. DSIP plasma concentrations also exhibit a rhythmic 24-h pattern the amplitude of which apparently depends on the magnitude of body-exercise i.e. daily activity. DSIP in humans was found also to exert a bell shaped dose response curve exhibiting an activating effect during awake states in situations conductive to sleep. Clinically and statistically significant effects upon sleep architecture were seen from 1h through up to 20h after injection; adverse effects were never observed. Single dose treatments of insomnia showed significant normalization effects of DSIP in all sleep parameters as did repeated administrations in chronic insomniacs. Daytime performance were found to improve after DSIP injections which at higher dose exerted a benefitiary effect in organic insomniacs. The peptide was able to suppress withdrawal effects in benzodiazepine addicts and normalized sleep patterns in narcoleptic patients. In summary DSIP is suggested not only to be a sleep promoting and maintaining peptide but a supra-modulatory active psycho-physiological "programming" substance.

Introduction

From 1963 to 1970, the possibility of humoral transmission of delta (SWS)-EEG sleep in rabbits by i.c.v. infusion of extracorporeal dialysate from blood of the sinus confluens of donors kept asleep by electrical stimulation of the ventromedian intralaminar thalamus has been established (1,2). From 1970 to 1977, we isolated, characterized and synthesized a nonapeptide called delta-sleep-inducing peptide (DSIP) responsible for this effect (3,4). Subsequently, intravenous administration of DSIP was shown to produce sleep in different animals lasting for hours. Analogs with exchanged amino acids in the sequence or shortening the peptide by one or two amino acids decreased or abolished the effect as did breakdown products suggesting specific structural requirements of the peptide (5). In contrast, sleep-induction per se was found to be species-specific, i.e. in cats, REM-sleep was predominantly enhanced (6).

The penetration of the blood-brain barrier by the peptide has been demonstrated and it was shown that unweaned rats are able to take up DSIP by the intestinal tract (7). The half-life time for proteolytic split-off of tryptophan by brain slices and homogenates is 15 min (8). Endogenous immunoreactive DSIP-like material in plasma, was found to occur partially in larger forms (carrier?) and thus protected from proteolysis (9). DSIP was shown immunohistochemically to occur in different regions of the rat brain A multivariate activity of the peptide was suggested by its interaction with acute and chronic stress as well as with drug effects such as morphine, d-amphetamine and barbiturates (10). An induction of MAO-A synthesis in the brain increased during progressed hibernation. Alcohol addiction produced a substantial decrease of the DSIP-concentration in rat brain. DSIP also produced specific electrophysiological effects on isolated neurons of rats and rabbits. We demonstrated a specific binding of DSIP in cultured nerve cells. The multivariate activity of the compound has recently been reviewed (12).

Dose-Response Curve

The fact that higher dosages above 30 nmol/kg body weight had no effect, led us to investigate the dose-response relationship after intracerebroventricular application of 2-12 nmol/kg DSIP. The result is depicted in figure 1.

In contrast to a pharmakon, DSIP exerted a parabolic dose-response curve with a rather narrow optimum at 6-8 nmol/kg. Identical dose-response curves were obtained after intravenous administration of the peptide. The optimum in the latter case was found at 30 nmol/kg body weight. Other authors demonstrated after subcutaneous administration also a parabolic dose-response curve which appeared to be flatter with an optimum ~120 nmol/kg DSIP (13).

The results suggested that the sleep-inducing property of the peptide was one effect out of a multivariate spectrum.

Circadian Rhythmicity (Locomotor Activity)

For sleep is an integral part of the centrally programmed circadian rhythmicity, we investigated the effect of the peptide upon the biorhythms of the locomotor activity and several biochemical parameters in rats. Four consecutive i.v. injections were made for 4 days between 17.00-18.00h whereby DSIP was administered. One set of experiments was carried out under normal 12:12h light: dark conditions. In a second experiment, DSIP was administered under continuous true-light conditions.

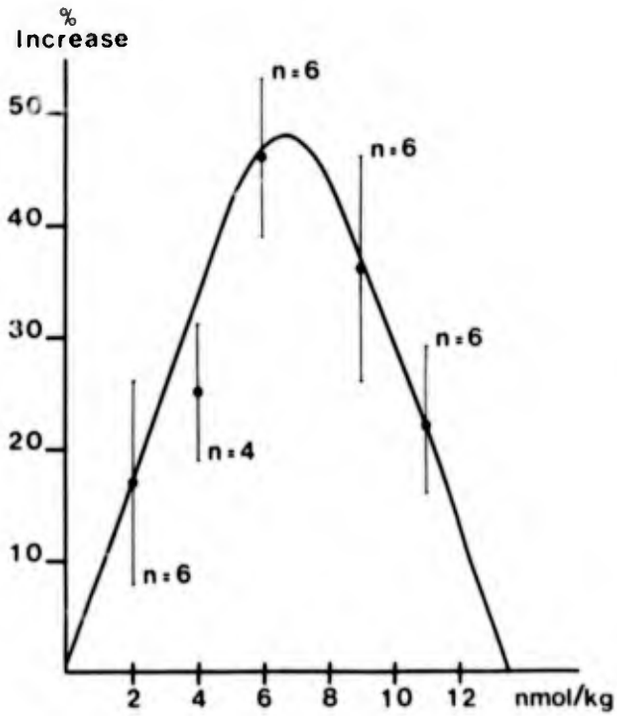

Figure 1: Dose-response curve (Delta-EEG-sleep) after i.c.v. administration of DSIP to rabbits.

In figure 2 the changes of locomotor activity of rats injected with 30 nmol/kg DSIP over 4 days under continuous true-light illumination (solid line) and under a normal 12:12h light:dark schedule (dotted line) are depicted. The curve indicates the percent changes of the activity of the test animals (n=12) compared to the internal control animals (n=12) taken as 100%. Both groups were standardized to their first (=baseline) day (not on the graph!). The usual light:dark sequence provides a strong "Zeitgeber" for the normal circadian locomotor behavior and possibly suppresses a clear influence of DSIP under those conditions. Constant illumination for 24 days eliminated the influence of the "Zeitgeber". In fact the spontaneous activity of our control rats from 18.00-06.00h in the constant illumination condition amounted to only 50-60% of the overall 24-hour activity whereas in the light:dark schedule this time period contained 80-85% of the daily activity. DSIP i.v. under constant illumination, as shown in figure 2 (solid line), produced more rapid and marked changes than during the day-night schedule (dotted line) starting with the first day of peptide injection. At the beginning, a decrease of activity for at least 12h was induced by DSIP which was followed by an enhancement of the relative activity for the next 8-12h. Relative to the internal controls (100% line), the increased activity during the "day" period and the decreased activity during the "night" hours were statistically significant. This increase of the relative motor activity was similar but more pronounced than that found under normal 12-hour/light:dark conditions (fig. 2, dotted line)(14).

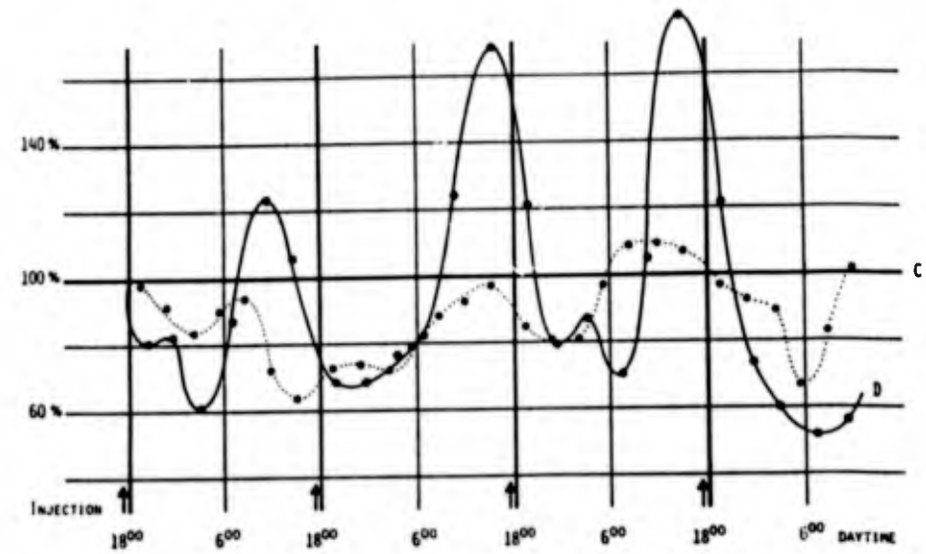

Figure 2: Quotient of the locomotor activity of rats injecte' with 30 nmol DSIP/kg over 4 days under continuous illumination (solid line). Dotted line: identical experiment under normal 12:12h light: dark conditions (14).

Biochemical Changes

In different experiments the influence of DSIP on the concentrations of brain neurotransmitters, serotonin (5-HT), dopamine, and norepinephrine, plasma proteins and hormones was investigated at four time points within the 24h following i.v. injection of 30 nmol/kg in rats. DSIP administered in the morning or in the evening, respectively, induced changes in nearly all measured parameters. Different effects were observed for different times of administration (15). The most marked changes were found in the level of serotonin during day-time as shown in figure 3. The morning administration of DSIP caused a significant decrease of 5-HT as compared to the NaCl control (open circles). Injection in the evening did not change the 5-HT concentration during night but a significant decrease vs control level occurred the following day.

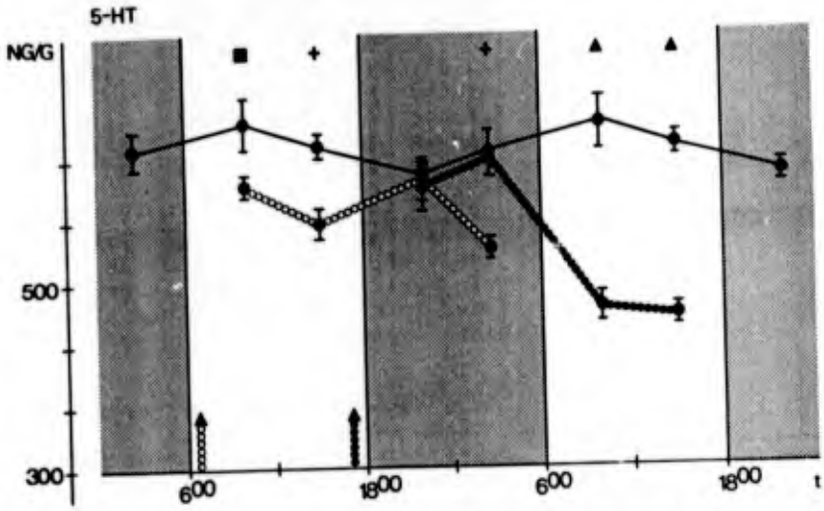

Figure 3: Content of 5-HT in rat brain at four different times of day. Solid line = saline controls. Open circles: rats injected in the morning (arrow), closed circles: rats injected in the evening (arrow). ■ = $p \leq 0.05$ + $p \leq 0.01$ ▲ $p \leq 0.001$ (t-test).

In figure 4, the influence of DSIP on the levels of prolactin in rat plasma are shown. A highly significant influence of DSIP was seen ($F_{1,76} = 9,03$, $p \leq 0.005$) but no clear impact was due to the time of injection ($F_{1,76} = 2,88$, $p \leq 0.1$). DSIP treatment lowered the scores at 22.00h in the dark period when control prolactin levels were high, after both morning (= A; not significant) and evening injection ($p \leq 0.05$). The 24h mean of the DSIP-treated animals given an evening injection (=B) was significantly below that of the controls ($p \leq 0.05$). A similar tendency ($p \leq 0.1$) after the morning injection, however, was not significant.

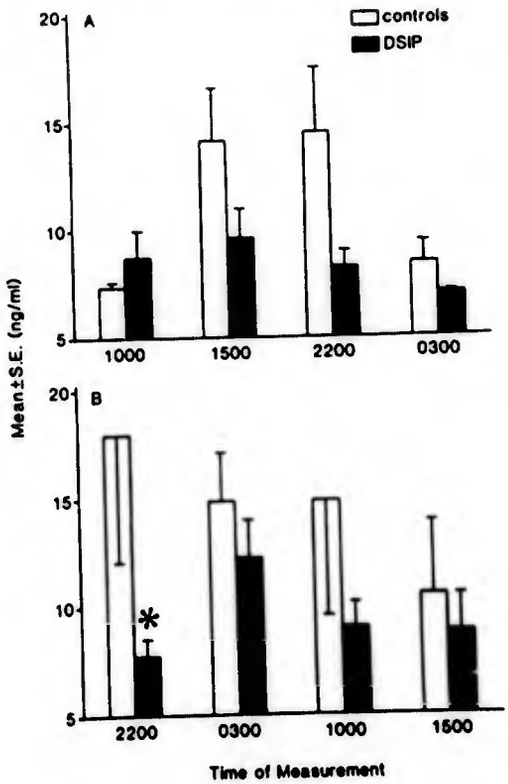

Figure 4: Influence of DSIP on prolactin levels in rat plasma. Controls were injected with saline only.

A distinct effect of DSIP on prolactin concentrations was thus obtained. Although prolactin levels in plasma may change several, times during 24h reflected by the controls A and B the mean scores of the DSIP treated rats were (except at one time point) lower than controls and the main influence of the peptide was highly significant.
Our results suggested that DSIP originally thought to be a sleep-peptide, also influences circadian rhythms. The peptide apparently is capable to shift or even induce locomotor activity of rats and influences the levels of neurotransmitters in rat brain or plasma concentrations of hormones again in a manner dependent on the time of day (14)

Further attempts to elucidate the influence of DSIP on circadian parameters led us to investigate serotonin-N-acetyltransferase, an enzyme of the pineal gland, which converts serotonin to N-acetylserotonin. The activity of serotonin-N-acetyltransferase (NAT; EC 2.3.1.5), has long been known to exhibit a strong circadian rhythm. Darkness induces a marked increase of the enzymatic activity that in the rat, for instance, can reach up to 60 times the level found during daylight (16). It was recently reported that this increase seems to be due to α as well as β-adrenergic agents working in a synergistic way (17). It was our goal to determine whether DSIP could influence NAT activity in the pineal and whether such an influence would be dependent on the time of day.

As shown in figure 5a and 5b the influence of DSIP on NAT activity depends on the time of day of the injection. Analysis of variance revealed that the time of injection by itself tended to have a significant ($F_{1,62} = 4.59$; $p \leq 0.07$) influence. The time of decapitation showed a strong main effect ($F_{3,62} = 15.12$; $p \leq 0.0001$) reflecting the marked increase of NAT activity during darkness compared to the low levels during light. All values obtained during light were significantly lower than the control score measured during the dark at 22.00h (Fig. 5a). Neither the main effect of the peptide by itself nor the interaction of time of injection by time of decapitation was significant. The highly significant ($F_{1,62} = 8.41$; $p \leq 0.01$) interaction between time of injection and effect of peptide, however, represents the marked reduction of NAT activity in the DSIP-treated groups during the night when the peptide was administered in the evening (Fig. 5b). This was also reflected in the significant three-way interaction of time of injection by time of decapitation by effect of peptide ($F_{3,62} = 3.02$; $p \leq 0.05$). The

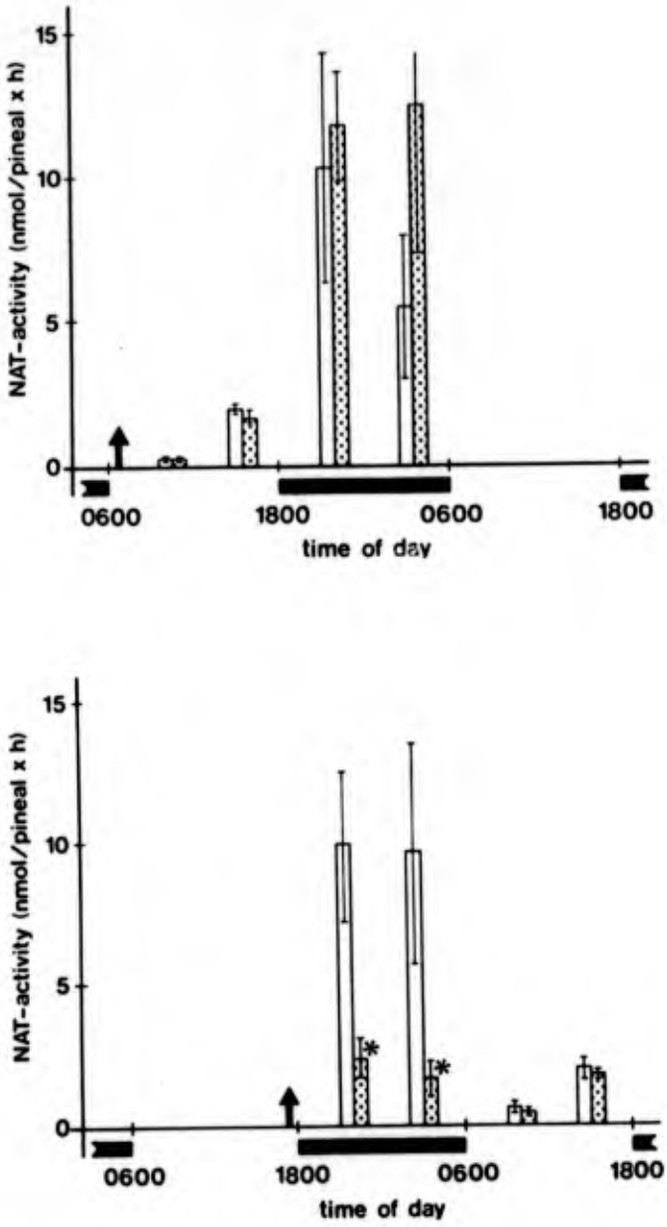

Figure 5a and 5b: Influence of DSIP on NAT activity at different times of day. Dotted bars = DSIP-injected groups; open bars = saline controls. Arrows = time of injection: morning (a), evening (b). Black bars = darkness. *p ≤ 0.05

direct comparison of the control groups with the DSIP-injected rats showed a significant reduction ($p \leq 0.05$) of NAT activity at 22.00h and 03.00h when the animals were injected in the evening (Fig. 6b). A tendency in the opposite direction was found at 03.00h when DSIP had been injected 21h earlier (Fig. 5a).
These experiments in animals suggest beside a species-specific sleep induction, effects of DSIP on different parameters which are related to circadian or other biological rhythms.

DSIP-Body Fluids

Since 1981 several laboratories developed radioimmunoassays for quantifying DSIP-like immunoreactive material (=DSIP-LI) in tissues and body fluids. During the past year we were able to raise specific antisera in rabbits for selectively determining DSIP immunoreactive compounds. We could confirm that DSIP immunoreactive material in plasma is mainly present in a macromolecular form. Only 5-10% or less were detected as free peptide. In human CSF 50% of DSIP/DSIP-P-LI was shown to occur in free form by column chromatography and ultrafiltration techniques. A major part of the peptide occurs in the free form in human urine in which none or little proteolytic degradation takes place.
However, in human milk during normal lactation DSIP values of 2.3 ± 0.12 with individual variations between 2 and 20 ng/ml were found. Twentynine percent of DSIP-LI was present as free form. A possible influence of the time of day was investigated in one subject. Pooling the data of the days with complete sampling revealed a circadian rhythm of DSIP-LI in breast milk as demonstrated in figure 6.
The main effect of time of day was highly significant ($F_{7,27} = 3.70$; $p < 0.01$), with the levels in the afternoon being higher than the morning.

To summarize, several studies have revealed that DSIP can influence different parameters within their biological rhythmicity. The fact that sleep is part of a circadian rest-activity cycle provides a basis for DSIP of influencing sleep in its frame of the circadian rhythm.

DSIP - Circadian Rhythmicity of Plasmalevels in Humans

DSIP was measured by a specific radioimmunoassay in blood-samples (heparin-plasma) taken from 5 volunteers in 30 min intervalls during 24h (Figures 7a and 7b)*. The experiments were done under two conditions for each of the subjects. In a first session daily activities, eating and smoking were allowed (Figure 7a). In the second session (one week after the first) the subjects were kept in bed and were not allowed to eat, smoke nor to exert any activity, but they were free to sleep at libidum (Figure 7b).
The DSIP time series obtained by RIA were first smoothed by moving average using five time points. In the next step each of the smoothed DSIP curves was normalized by division with its mean DSIP value thus creating a new curve around a mean value of 1. In order to obtain a less "subjective" picture of the circadian variations of DSIP for each condition, time points of the normalized curves of all subjects were averaged and standard deviation was calculated. Figure 7a: At 10 o'clock in the morning, a slight increase occurs. Around 14.00h a first decrease of DSIP-like material is seen. The time point coincides with known decreases in vigilance and concentration capacity during the day.
*The plasma samples were provided by Dr. P. Schulz, Division of Clinical Psychopharmacology, University, Department of Psychiatry, Geneva, Switzerland

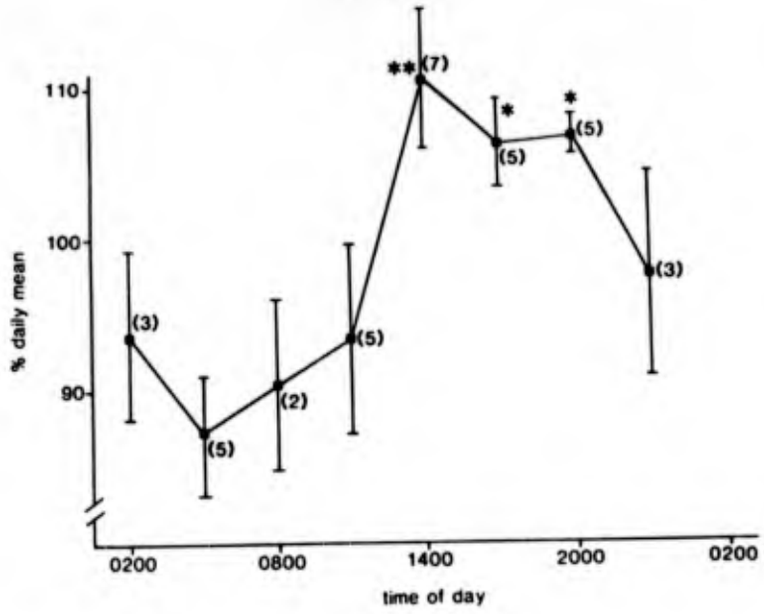

Figure 6: Influence of time of day on the concentration of DSIP-LI in milk. Data from several days were pooled and the mean taken as 100%. In parentheses = number of values (*, $p \leq 0.05$, **, $p \leq 0.01$).

After a broad shoulder of high DSIP concentrations, the onset of a market fall occurs at 20.00h which keeps on decreasing until 23.00h to midnight = sleep onset. From 4 o'clock in the morning DSIP levels are again built up i.e. production overshoots consumption, in order to reach the morning peak of the next day. Normal sleep EEG patterns were recorded for all 5 subjects, from 23.00h to 7 o'clock. Apparently sleep induction and maintenance by DSIP occurs during increased consumption of plasma concentration which is built up during "recovery" in the last third of the night. This assumption is sustained by the DSIP-LI pattern obtained from the same 5 volunteers during bed rest (Figure 7b) the rhythmicity not anymore maintained by the daily activity is although still present, visibly smoother. Peaks are less pronounced and broader as compared to Figure 7a.

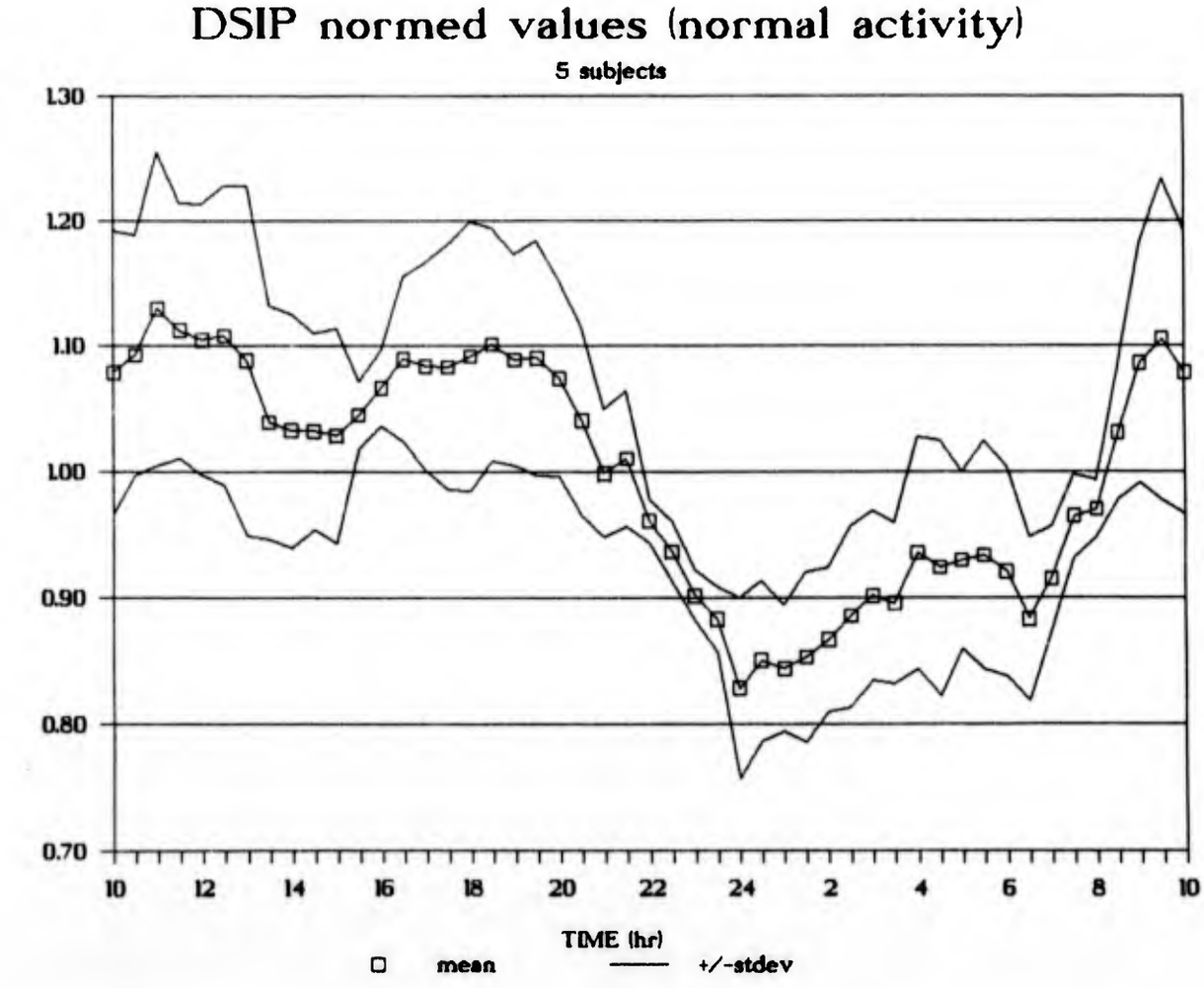

Figure 7a

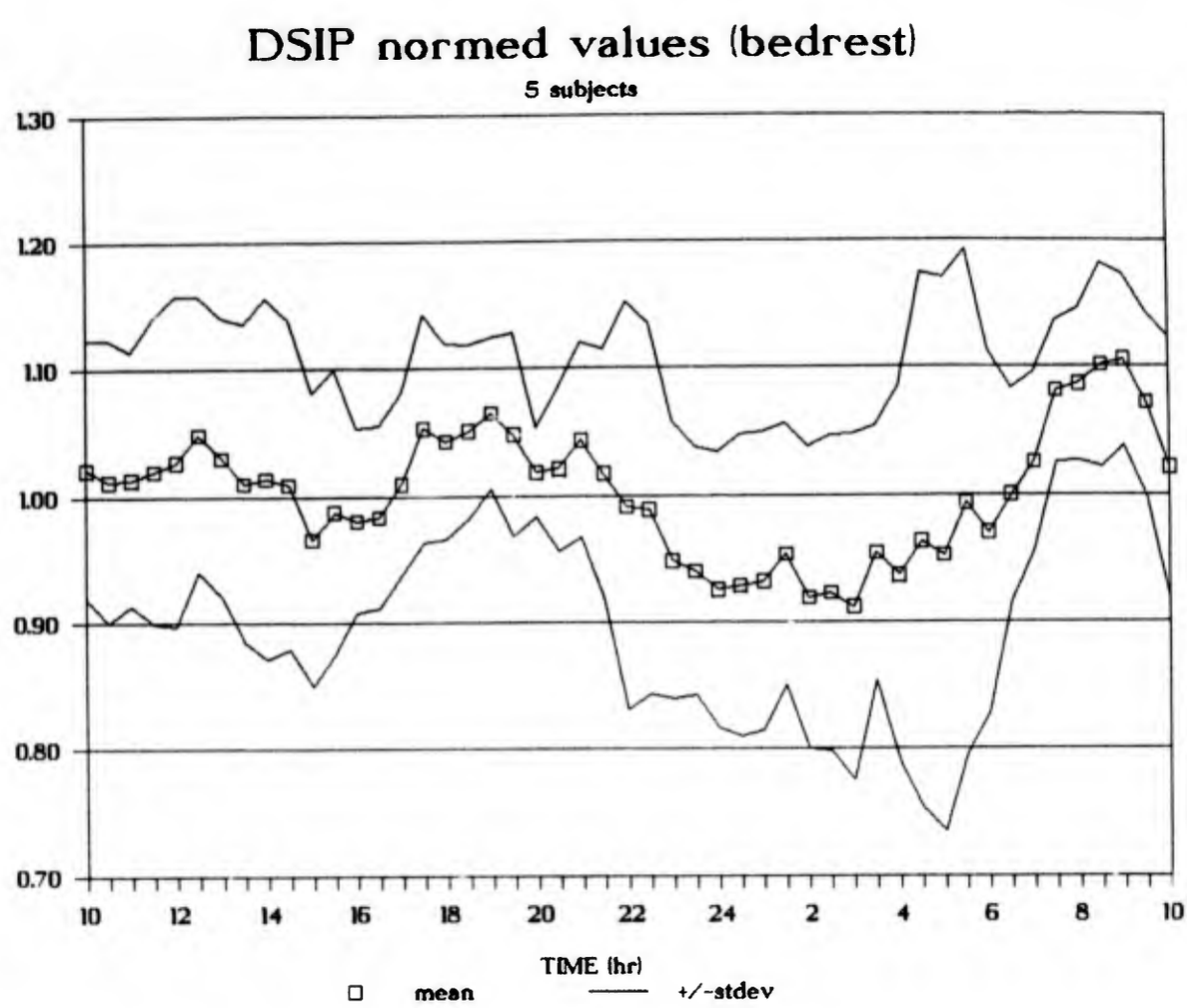

Figure 7b

Pharmacological Properties of DSIP

This section reports what has been established by human experiments on the basis of prior findings in animals. The latter had shown a bell shaped dose-response curve for sleep inducing effects with an optimal dose of 30 nmol/kg b.w. for iv injections, and - for this mode of administration - a latency of effects of approximately one hour (17). Our findings in man are the following:

(1) An effective dose for promotion of sleep by iv injection of DSIP is 25 - 30 nmol/kg b.w., i.e. 1.5 mg/70kg. At this dose level, the maximum effect is achieved by injecting DSIP slowly over 4 to 6 minutes.

(2) At that dose level, DSIP exhibited activating effects during an active awake state besides promotion of sleep in situations conducive to sleep. Some observations suggest that the activating effects might predominate at higher daily doses.

(3) Clinically and statistically significant effects were seen from 1 hour through up to 20 hours post injection.

(4) Adverse effects have never been observed in a total of 1000 single and repeated injections, the majority of them under immediate polygraphic recordings and with pre- and post-treatment laboratory examinations.

Single Dose Treatment of Insomnia

In a study with six severe insomniacs (18,19), DSIP (25 nmol/kg b.w.) was injected once or twice, respectively, in a randomized assignment within a series of five successive nights that were polygraphically recorded. On non-DSIP nights, placebo injections were made under double-blind conditions. The lights were turned off and recordings started immediately after the injections. DSIP had a number of statistically significant effects on variables of total night sleep: The duration of the combined REM sleep, slow-wave and spindel sleep increased by a mean of 32.25 minutes ($p < 0.01$), and likewise did the sleep efficiency increase by 8.1% ($p < 0.01$); the number of arousals from sleep was reduced by a mean of 3.6 per hour ($p < 0.05$); in the distribution of the sleep stages, a reduction of the proportion of stage 1 by 4.4% ($p < 0.025$) and a tendency for a higher proportion of REM sleep was found. Subjective evaluations showed a tendency to feeling more relaxed after sleep with DSIP and towards increased daytime activity. Though these effects were not statistically significant, they certainly confirmed the previous finding (20)), that DSIP does not depress cortical vigilance in the sense of sedation, and thus showed definitely no hang-over effect.

A stepwise analysis of the sleep recordings, made hour by hour, revealed that the latency for effects of DSIP on sleep was some 60 minutes following injection. It was suggested

that this time lag, which had also been found for intravenous injections of DSIP to rabbits (17), might have been the reason for the lack of DSIP effects on sleep onset latency in that study, where DSIP was injected immediately before the sleep recordings. Furthermore, it seemed possible that effects of DSIP on variables of total night sleep could become stronger with advanced administration of DSIP.
In the latest study, performed in a group of 7 male and 7 female insomniacs with a mean age of 45 years, DSIP at a dose of 30 nmol/kg b.w. was therefore given one hour prior to bed-time. This mode of treatment significantly shortened sleep latency and was very powerful in reducing disturbances of sleep throughout the night as well.

Table 1. Single injections to 14 insomniacs

	Baseline	DSIP		
	mean	mean	effect prc.	sign.
Sleep efficiency (%)	63.8	76.8	+ 20	0.005
Total sleep time (min)	313.0	363.1	+ 16	0.005
Sleep latency (min)	58.4	38.9	- 33	0.025
Wake after sleep onset (min)	120.8	78.0	- 34	0.025
Awakening index	2.0	1.1	- 50	0.000
Arousal index	7.2	5.9	- 22	0.025

Table 1 shows the responses in the main insomnia variables, i.e. sleep efficiency and total sleep time for global effects, sleep latency for induction, and three variables characterizing sustained sleep after onset. The awakening index is the number of spontaneous awakenings per hour of sleep, arousal index includes transitions from sleep to stage 1 and movement time besides awakenings. It is clear from these data, that DSIP significantly improved both induction and maintenance of sleep. The resulting increase of mean total sleep time was 50 minutes.
The treatment sequence was placebo - DSIP in this latest study, because it was part of a short-term treatment series. Therefore, it could be argued, that the effects were due to adaptation and/or placebo effects. In order to test this possibility, the data of a matching control group with continued placebo injections were analysed. They showed no progressive changes and no significant differences between night sleep on baseline and on following placebo nights. This control trial thus not only corroborated the results of this large group study with single administration, but is also important for the evaluation of repeated administrations to be reported in the next section, where a sequential study design was required by the specific hypotheses.

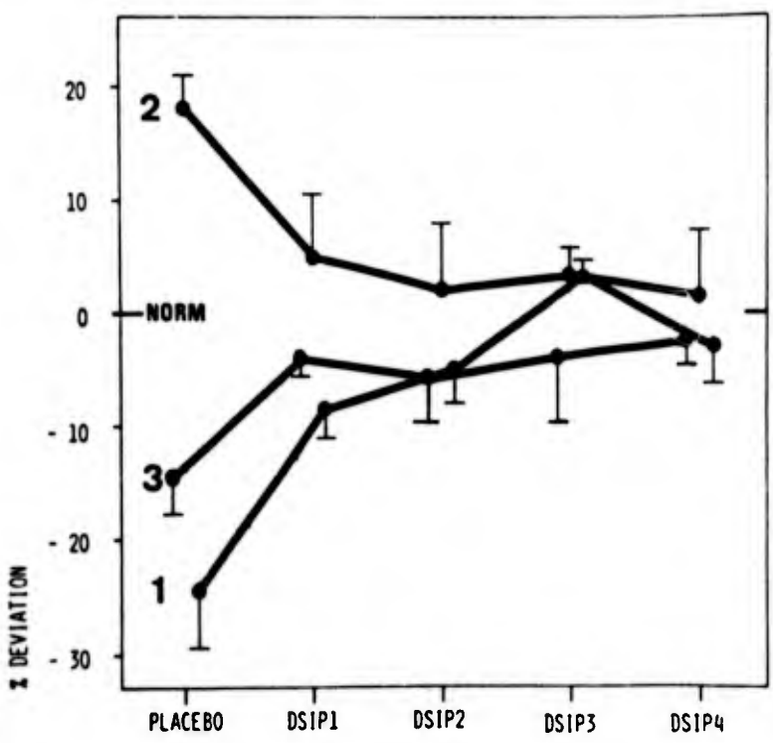

Figure 8

Repeated Administrations to Chronic Insomniacs

The first repeated injections of DSIP were given in a pilot study to four chronic insomniacs, 3 female and 1 male middle-aged Ss. DSIP efficaciously improved sleep, showing a build-up of these effects over the first three out of four consecutive injections with a final increase of mean total sleep time by 90 minutes. It proved difficult to evaluate differential effects on sleep structure, because variation due to age and sex factors was substantial in this small group. Therefore, the data were considered with respect to normative values (21) and depicted as percentage deviation from normal data. Figure 8 represents three variables that were particularly prominent by their pathology under baseline conditions, i.e. (1) sleep efficiency; (2) waking + stage 1; (3) REM proportion of total sleep.

The small standard deviations indicate, that the group was homogenous as to type and degree of sleep disturbance, and that the Ss responded equally well to treatment. Evidently, the first DSIP injection yielded the main effect and additional DSIP injections built up further improvements, finally reaching complete normalization of sleep.

Insomniacs of this pilot study and of several single case studies with repeated DSIP treatments reported sleep improvements overlasting the treatment period for one or more nights. A study with a large group of relatively unselected insomniacs was therefore designed such as investigating the effects of the 1st and 7th DSIP injection of a one week treatment period and the first withdrawal night as well. The results of the first, i.e. single injection, have been presented above. The results of the final treatment night and first withdrawal night are reported in table 2:

Table 2. One week treatment of 14 chronic insomniacs

	Baseline	DSIP7			Withdrawal		
	mean	mean	effect prc.	sign.	mean	effect prc.	sign.
SE (%)	63.8	81.2	+27	.000	77.8	+22	.000
TST (min)	313.0	385.0	+23	.000	376.2	+20	.000
Latency (min)	58.4	27.6	-53	.001	35.7	-39	.005
WASO (min)	120.8	65.6	-46	.000	73.2	-39	.000
Awakening Index	2.0	1.1	-45	.000	1.2	-40	.005
Arousal Index	7.2	5.8	-19	.005	6.3	-13	.025

The seven consecutive DSIP injections proved very efficacious for the treatment of chronic insomnia, yielding a mean increase of total sleep time by 72 minutes and an improvement of sleep efficiency by 27 percent of pretreatment baseline values. The responses were all statistically highly significant as represented by the p values for comparisons versus baseline (non-parametric Wilcoxon matched pairs signed rank test). These effects were slightly attenuated in the first withdrawal night after the treatment period. However, sleep in withdrawal night was not statistically significantly different from DSIP7, nor was the latter different from the first DSIP night. The time course, visualized in figure 9 can be characterized as follows:

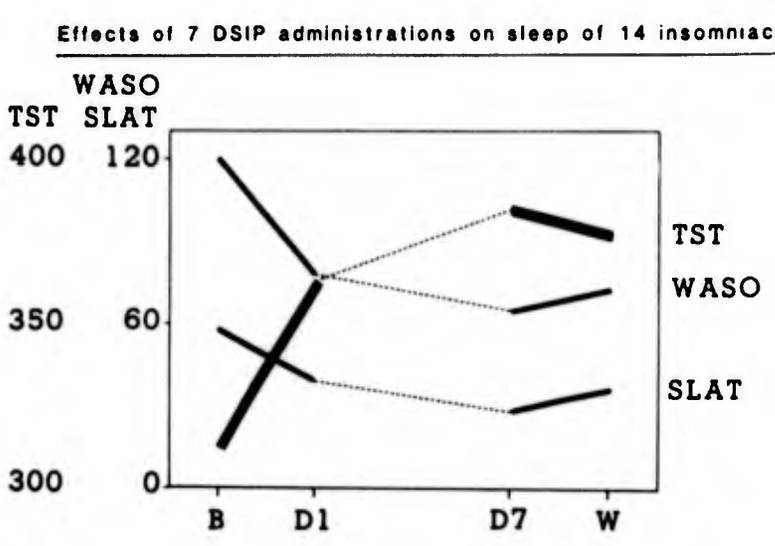

Figure 9

Main treatment effects occured with the initial dose, six more consecutive injections further improved sleep by rougly one third, and sleep remained actually the same in the first withdrawal night thereafter.
DSIP did not affect the sleep structure in this group which showed approximately normal sleep stage proportions before treatment. DSIP did affect the cyclic aspects of sleep, i.e. number of REM periods, REM sleep latency, mean inter-REM intervals, but this was not a primary effect, as a special investigation revealed, but mediated by reductions of intermittent wakings.
A marginally significant increase of proportion of REM sleep occured at the beginning and end of the treatment period. Since we have observed effects of DSIP administration on REM sleep in various experiments, it might well be that a particularly close relation exists between DSIP functions and REM sleep.

Effects on Daytime Performance

Trends for increased daytime activity were found from the beginning of our studies on DSIP. The first investigation (20), where DSIP was administered by slow infusions in the morning, clearly demonstrated that DSIP had no sedative, i.e. centrally depressant, actions as evidenced by performance tests and power spectral analysis of the EEG 2 hours after administration. As far as insomniacs are concerned, a full day program of performance tests and intermittent rest periods was applied to the group of 14 Ss on baseline and after 6 injections of 30 nmol DSIP kg. Sleep in those rest periods significantly increased, and performance did so in 6 out of 8 tests; none of them showed deteriorations.

Table 3.

Daytime performance following repeated DSIP administrations

Test	Percentage improvement	Significance p <
Auditory Vigilance	28	0.1
Digit Symbol Substitution	31	0.000
Addition	25	0.05
Visual Search	36	0.000
Line Judgement	23	0.000
Baddeleys Reasoning	55	0.000
Word Detection	4	n.s.
Line tracing	22	0.05

It is possible, that these effects were mediated by more efficacious night sleep and daytime rest, but it seemed also possible that they were, at least in part, a direct effect of DSIP. To test this possibility in a pilot study, two Ss were examined by the d2 and Line tracing tests 3 hours after DSIP or placebo injections, administered in the morning with no possibility for rest between injection and performance tests. A dramatic sudden increase of performance occured with the first DSIP injection, suggesting that DSIP administration may be promoting alertness directly and independent of its action on the functions of sleep to a clinically significant degree (22).

Special Case Studies

A number of case studies were carried out to check the possible effects of DSIP in various conditions of pathology, and possible differential effects of various dosages and/or times of administration. In addition, these pilot studies aimed a generating hypotheses on the actions of DSIP in man.

Injections at various times of day

Two neurotic insomniacs were given six injections of 25 nmol/kg b.w. each at 9 a.m. (2 x 3 consecutive days with 2 days free interval). The treatment period was preceded and followed by placebo periods. Since there was no clear carry-over effect to the final placebo period, both placebo periods were combined to establish baseline measures. The two periods of three nights each under treatment showed significant improvements of sleep as compared to baseline, with sleep efficiency +16 %, amount of waking plus stage 1 -42 %, arousal density -64 %. Enhancement of REM sleep occured mainly in the first part of treatment.

Another patient, who had participated in a sleep laboratory study and who's subjective evaluations of sleep had shown to be reliable enough to indicate possible treatment effects, has been given DSIP for 3 weeks in an out-patient treatment setting. Injections of 25 nmol/kg b.w. in the evening improved sleep and daytime activity. Earlier injection time, i.e. at 3-4 p.m., yielded similar results. Two daily dosages, i.e. in the morning and late afternoon, yielded even higher daytime activity, but sleep was worse than on baseline with this mode of 2 x 25 nmol/kg per day. These data indicate, that the optimal dose of the well-known bell-shaped dose response curve is at one daily dose of 25-30 nmol/kg b.w. for promotion of sleep functions, whereas the curve might be broader for sustaining daytime activity.

DSIP in organic insomnia

In a case of extreme insomnia due to midbrain and brain-stem lesions (23), the dose of DSIP was gradually increased over 3 weeks to 70 nmol/kg/day. Total sleep time was nearly doubled and decreased very slowly after the treatment period, but did not return to pretreatment levels within 2 weeks. Concurrently, daytime activity was improved. The plasma concentration of endogenous DSIP was determined before the treatment period and was rather high as compared to preliminary data of normals. It seems, that productive sites were intact, but that higher amounts of DSIP were needed for sleep functions in this case of organic lesions in the brain.

DSIP in withdrawal from Benzodiazepines

DSIP proved clinically efficacious in suppressing withdrawal symptoms of opiate addicts and alcoholics (24). Therefore, we have recorded sleep of two patients in withdrawal from long-term use of Benzodiazepines and with DSIP administration (25 nmol/kg) on 3 successive nights. One male patient of 69 years of age responded very well to the treatment, but one female, hysteric and depressed patient of 49 years of age showed moderate, but inconsistent responses, probably due to interference of psychological problems.

DSIP in narcolepsy

The rationale for testing DSIP administration in a case of narcolepsy was based on the clinical findings, that DSIP had both activating and sleep promoting properties, and that it proved also effective in cases of organic or pharmacological sleep disturbance. Though the cause of idiopathic narcolepsy is now known, this disease may have some organic basis considering its hereditary components. Our case was a 35-year-old male patient with documented narcolepsy for more than 10 years. Prominent symptoms were sleepiness and sleep attacks during daytime and some insomnia at night. Cataplexy was absent. The investigation included 3 identical weeks with daily self-assessments and, at the end of each week, one night of polysomnography and a day in the laboratory for the Multiple Sleep Latency Test and testing sustained performance on a battery of computer directed tests. Treatment consisted of daily 25 nmol/kg DSIP injected in the

evening for one week and in the morning for another week. The main treatment effects were on daytime performance in terms of lower sleepiness, fewer sleep attacks, and higher performance. However, these effects faded in the afternoon when injections were given on the prior evening, suggesting that DSIP was effective on awake activity for some 18 hours post injection. Night sleep was only affected by injections in the morning in the direction of less fragmented, but shorter sleep, which seemed to be appropriate to the individual needs of the patient, since he rated his sleep quality much better under these conditions. The overall clinical assessment was better for morning than for evening injections of DSIP.

Effects on neurotic behavior

The majority of those patients receiving repeated administrations of DSIP spontaneously reported after the studies, that they had made positive experiences in the sense of better managing daily stress. The effect was clear in 8 Ss and slight in another 3 Ss out of 14 Ss in whom post-study follow-up observations were made. Therefore, the study in two patients on which we have already reported some data above, was carried out. They were in a psychotherapeutic ward and were given 6 DSIP injections in the morning of a two week trial, which contained pre- and post-treatment placebo periods. The patient completed self-rating scales, and they were evaluated by two psychotherapists independently, each day under double-blind conditions. The general results of these assessments were: Improved coping with emotional problems and intensified psychotherapeutic work. Therefore, we have suggested (22), that DSIP might improve ego functions in neurotic conditions (25).

Tentative Conclusions

DSIP is safe in single and short-term repeated administrations. However, the intravenous injection is a factor severly limiting a broader clinical investigation.

The efficacy for the treatment of psychophysiologic / primary insomnia was demonstrated in two completely independent series with a total of 20 Ss and in a number of pilot studies with another 7 Ss. All these patients had presistent / chronic insomnia. On the one hand, this type is particularly difficult to treat, and one tentative conclusion would therefore be that DSIP is an especially powerful treatment. On the other hand, it could be possible that chronic forms of insomnia show a specific responsiveness of DSIP. Some support to the latter speculation may be seen in the findings, that insomnia due to brain lesions or withdrawal from Benzodiazepines did respond to administration of DSIP, the significance of those pilot trials being that diseases were influenced by administration of DSIP, which most probably involved disturbances of biological functions of the brain. It is our assumption - based on ample clinical experience - that biological regulations are affected, on a functional level of course, in chronic insomnia, too.

Increased alertness and higher performance are actions of DSIP which seem to open a completely new principle for the treatment of sleep disorders, the clinical implications of a possible therapy in the future with DSIP being obvious. Repeated observations in insomniacs and the first trial with administration in narcolepsy indicate, that the activating effects of DSIP are most probably not only mediated via improvement of sleep, but that they are primary effects as well as promotion of sleep. As much as physiologic systems for the regulations of sleep and arousal systems are known today, as little is known about coordinating systems that must, of course, exist in the brain in close relation to other functions involved in behavior rather than physiology. Our observations in man suggest, that DSIP is one of probably a number of neuromodulators involved in this high level functions. which I call behavioral coordinations. This is consistent with recent findings on the distribution of DSIP containing neurones and binding sites. Our observations in the organic case and the notion of higher stress tolerance of neurotic patients through DSIP administration support this view from clinical grounds.

In an attempt to summarize and conceptualize our present knowledge, we suggest to consider DSIP as a neuropeptide involved in the regulation of complex behavioral patterns rather than single physiologic systems. As a working hypothesis, we assume that DSIP is needed for various kinds of adaptive functions and thus serves - psychodynamically speaking - ego functions.

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Discussion

Nicholson, UK

. . (not recorded). .kind that you were using each time because, for instance, with the pilot he came into your clinic and then his sleep improved on the second night, that was without use of the drug. And then the drug was used for seven days and also with the other improvements in sleep that you used and improvements in performance, how were you able to exclude the possibility that the effects on performance were not learning curves? And that the effects on sleep were not just the simple improvements in sleep that you observe with placebo when people are in sleeping clinics?

Schoenenberger, FR

In the clinic, as you know, you cannot do placebo, at least not in a private clinic where people pay, you cannot do real placebo crossover or control crossover studies. To answer your first question, we tried to eliminate learning effect by preceeding training sessions for the psychological testing. As for the psychological measured paramenter, trait and special state parameters, we are dealing with patients and all of the patients who are coming to us are in these measured parameters underneath of the standard normality. And we don't take them into the study if they didn't have to sleep, but one with Parkinson's. People who don't go from below or to within pathological to out to normal values. This is the only real control beside these peole were treated between three and 15 years by acupuncture and orthogenic training and every drug you can imagine and they consume quite a lot of trnaquilizers, psychopharmacols, sleeping pills which we withdraw from one day to another. So we are dealing with this population. The improvement is impressive. That's all I can say about it now. This is preliminary data, we opened the center in June. The first 21 patients took in as they came.

PRESENTATION D'UN NOUVEAU STIMULANT : LE CRL 40476

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RESUME

L'emploi de stimulants constitue une des approches possibles du maintien de la vigilance au cours d'opérations soutenues de longue durée. L'efficacité et l'innocuité d'un nouveau stimulant le CRL 40476 sont évaluées chez le macaque rhésus. Les mesures d'activité nocturne, ainsi que l'interprétation d'enregistrements électroencéphalographiques mettent en évidence un effet anti-sommeil puissant sans désorganisation de la structure du sommeil. Les études d'innocuité tant végétative que comportementale soulignent l'absence d'effets secondaires, en particulier de type amphétaminique, aux doses utiles pour le maintien de l'éveil. L'expérimentation opérationnelle pourrait être abordée après définition préalable des doses et fréquences d'administration efficaces sur l'homme sain.

I - INTRODUCTION

Le contrôle de la vigilance, en situation opérationnelle, peut, d'un point de vue théorique, faire appel à trois approches. La première tente de prolonger l'état de veille par l'action d'une substance stimulante (1). La seconde consiste à induire, au moment opportun, pour une durée déterminée, et au moyen d'un sédatif un sommeil réparateur (2). Enfin, la troisième approche vise à une manipulation intégrale des alternances de veille et de sommeil par les mises en jeu successives d'un stimulant et d'un sédatif. Dans ce dernier cas l'utilisation d'antagonistes neurobiologiques offrirait la solution idéale.

Ces conceptions théoriques se heurtent dans la réalité pratique au caractère relativement limité des possibilités pharmacologiques actuelles. Cependant la mise en jeu d'une benzodiazépine à courte demie-vie, par la RAF au cours du conflit de l'Atlantique Sud, dans le but de faciliter la récupération des équipages, a constitué une démonstration convaincante de la validité de l'approche consistant dans l'induction contrôlée du sommeil par un sédatif (3). Malheureusement cette voie demeure de perspectives limitées. En effet, elle suppose la possibilité d'octroyer quotidiennement des périodes de repos total aux combattants.

Or les situations stratégiques et tactiques actuelles peuvent impliquer un engagement total et continu des moyens pendant des périodes de trois à quatre jours. En ces circonstances le recours à des stimulants devient pratiquement obligatoire si l'on veut conserver, aux personnels, un niveau optimal d'efficacité.

En 1983 à l'occasion du colloque consacré aux "Opérations aériennes intensives soutenues considérées sous l'angle de la physiologie et de la performance", le MC KLEIN a précisé, les conditions d'emploi d'un psychostimulant dans un cadre opérationnel. Il a défini, par ailleurs, une méthode d'évaluation de ces substances, faisant appel à un modèle primate. Enfin il a rapporté les résultats des études conduites dans notre laboratoire soulignant, en particulier les aspects prometteurs d'une nouvelle molécule, dérivée de l'ADRAFINIL, le CRL 40028 D1 ou CRL 40476 (1).

Après avoir rappelé les propriétés pharmacologiques de cette substance mises en évidence chez les rongeurs, les données recueillies chez les primates et visant à définir les limites d'efficacité et d'innocuité seront développées dans une perspective d'extrapolation à l'homme.

II - PROPRIETES PHARMACOLOGIQUES GENERALES DU CRL 40476

L'étude des propriétés pharmacologiques du CRL 40476, chez les rongeurs, met en évidence les caractéristiques générales d'un stimulant : hypermotilité, inhibition du sommeil barbiturique, reprise des comportements d'évitement après épuisement des sujets ou performance améliorée dans les épreuve dites de "progressif ratio". Ces traits propres aux stimulants ne sont pas accompagnés, aux doses utiles, d'effets amphétaminiques tels que les stéréotypies ou la toxicité de groupe (4).

L'étude plus précise des mécanismes d'action conduit à l'hypothèse d'une intervention à deux niveaux, selon la dose administrée. Aux doses faibles et modérées, prédominerait un effet noradrénergique central post-synaptique. Aux doses élevées le CRL 40476 provoquerait la libération de la dopamine du pool de réserve fonctionnel, ainsi qu'une libération de sérotonine (4).

III - EVALUATION CHEZ UN PRIMATE DE L'EFFICACITE DU CRL 40476 EN TANT QUE STIMULANT

Cette évaluation fait appel à deux méthodes, l'une est de spécificité limitée, proche de l'expérimentation sur rongeurs, et de mise en jeu aisée (5). L'autre, se caractérise par une grande spécificité, par un niveau élevé de fiabilité dans l'extrapolation à l'homme, mais aussi par des impératifs techniques particulièrement astreignants (6). La première fait appel à l'enregistrement de l'activité nocturne des macaques, la seconde à l'évaluation de l'état de vigilance de ces animaux par les techniques électroencéphalographiques.

31 - EFFETS DU CRL 40476 SUR L'ACTIVITE NOCTURNE DES MACAQUES RHESUS

- Méthode

Le principe général de l'épreuve consiste à comparer sous placebo et après traitement l'activité nocturne de macaques maintenus individuellement dans leurs cages de maintenance, ces derniers étant placés dans un environnement le plus homogène possible et soumis par ailleurs à un éclairage cyclé. Les mouvements des animaux sont détectes par perturbation d'un réseau d'ondes stationnaires ultra sonores. L'activité est mesurée par sa durée et non par son intensité. Chaque nuit ou partie de nuit peut être caractérisée, alors, par un pourcentage de temps consacré à une certaine activité motrice (7).

Quatorze macaques rhésus, adultes, mâles ont été utilisés dans cette expérience. Huit ont reçu P.O. quatre doses successives de 22,5 $mg.kg^{-1}$ de CRL 40476, six deux doses de 45 $mg.kg^{-1}$, et quatre deux doses de 90 $mg.kg^{-1}$. (8)

- Résultats

Les résultats obtenus (8) font apparaître, pour l'essentiel :

1. Un effet stimulant significatif dès la dose de 22,5 $mg.kg^{-1}$, particulièrement marqué pendant la première partie de la nuit.
2. Un effet proportionnel à la dose administrée.
3. La persistance, limitée, d'un effet post-traitement après administration de 90 $mg.kg^{-1}$.

Cette augmentation de l'activité nocturne n'est accompagnée ni d'effets anorexigènes, ni de perturbations apparentes des principaux paramètres végétatifs. Par contre à la dose de 90 $mg.kg^{-1}$ apparaissent des mouvements de stéréotypie.

Cette première épreuve, dont l'absence de spécificité a été indiquée dans le paragraphe précédent, ne permet pas de distinguer, en particulier, les phases d'éveil calme des phases de somnolence. Son objectif essentiel consiste à réaliser, à peu de frais, une évaluation grossière des propriétés stimulantes d'une molécule chez les primates. Elle fixe simplement les premières bornes de l'efficacité et de l'innocuité de la substance étudiée.

32 - EFFETS DU CRL 40476 SUR LA VIGILANCE DES MACAQUES RHESUS

- Méthode

La méthode d'évaluation des effets du CRL 40476, sur la vigilance du macaque rhésus fait appel aux techniques classiques d'études électrophysiologiques du sommeil (9).

Trois paramètres essentiels sont pris en compte : l'électrocorticogramme, l'électrooculogramme, l'électromyogramme. Les données fondamentales sont complétées par l'observation des animaux à l'aide d'un circuit de télévision capable de fonctionner même en éclairage très réduit. Pendant les enregistrements, les animaux , chroniquement bioinstrumentés, séjournent dans un environnement contrôlé et dont l'éclairage est cyclé. Ils sont, par ailleurs, maintenus sur un siège spécialement développé qui autorise la posture naturelle de sommeil propre à leur espèce (10).

Après interprétation, par un expérimentateur entraîné, les données relatives à l'éveil et aux différents stades de sommeil sont traitées par un microordinateur selon un programme standard. Compte tenu de la durée des enregistrements et de la lenteur relative de leur interprétation ce type d'expérience se révèle particulièrement astreignant.

Aussi l'évaluation des effets du CRL 40476, a été conduite en deux temps. Dans un premier temps les effets globaux et la dose efficace ont été déterminés après enregistrement de deux macaques rhésus, adultes, mâles, pendant les nuits suivant trois administrations de deux doses : 22,5 et 45 $mg.kg^{-1}$ (P.O.). Soit un total de 320 heures d'enregistrement : 12 nuits contrôles, 12 nuits sous traitement, 16 nuits post-traitement (11). La qualité des résultats obtenus dans cette première phase a conduit à une seconde étude plus extensive faisant appel à 4 macaques rhésus adultes, mâles, enregistrés cette fois jours et nuits et recevant quatre administrations de la dose seuil efficace : 22,5 $mg.kg^{-1}$ (P.O.). Cette deuxième phase représente 1152 heures d'enregistrement : 16 nycthémères pré-traitement, 16 nycthémères sous-traitement, 16 nycthémères post-traitement (12).

- Résultats

La première expérimentation montre que l'administration à 17 heures de doses de CRL 40476, égales à 22,5 et 45 $mg.kg^{-1}$ (P.O.) conduit à une insomnie totale dans les 9 à 12 heures qui suivent. Cette insomnie induite pendant trois nuits consécutives s'accompagne après arrêt du traitement d'un phénomène de récupération proportionnel à la dose administrée (11).

Par ailleurs la dose de 22,5 $mg.kg^{-1}$ (P.O.) apparaît comme une dose suffisante pour provoquer 9 à 12 heures d'insomnie sans pour celà induire de phénomènes de récupération trop importants. Cette dose est alors choisie comme dose de référence chez le macaque rhésus.

La seconde étude élargit et confirme globalement les résultats de la première. De manière plus précise elle conduit aux conclusions suivantes (12) :

1. Le CRL 40476 administré à la dose de 22,5 $mg.kg^{-1}$ possède des propriétés éveillantes particulièrement marquées pendant les 9 premières heures suivant son administration.
2. Ces effets éveillants ne désorganisent ni la structure du cycle nycthéméral de vigilance ni la structure du sommeil. En effet dès que le sommeil réapparaît, en fin de nuit, les différents stades de sommeil, dont le sommeil paradoxal, sont retrouvés.

3. La vigilance diurne suivant les nuits avec privation de sommeil est caractérisée par une organisation identique à celle suivant les nuits témoins, ainsi que par une augmentation de l'éveil.
4. A l'issue des quatre nuits avec privation importante de sommeil seule la première nuit post-traitement est marquée par un phénomène de récupération discret (réduction du stade 2 au profit du stade 4). L'absence de "rebond" à propos du sommeil paradoxal distingue significativement, à cette dose, le CRL 40476 des amphétaminiques et souligne son aptitude à respecter la physiologie du sommeil.
5. Bien que les animaux sous traitement aient été maintenus à un niveau global de vigilance de type diurne pendant 4 jours consécutifs, aucun trouble comportemental et aucun trouble végétatif n'ont été observés.
6. Les différences de sensibilité individuelle constatées à propos des données relatives à chacun des sujets apparaissent comme de nature quantitative et non qualitative. Elles demeurent par ailleurs dans des limites d'efficacité tout à fait acceptables.

33 - CONCLUSIONS

En conclusion à cette étude chez le macaque rhésus de l'efficacité du CRL 40476 en tant que substance éveillante les points suivants doivent être soulignés :

1. A la dose de 22,5 $mg.kg^{-1}$, le maintien et même l'amélioration de la vigilance diurne, malgré l'induction d'une insomnie nocturne importante, et bien que le CRL 40476 soit administré à 17 heures, apparaît comme un résultat original particulièrement intéressant.
2. Ce type d'action confirme chez le macaque rhésus, la nature très probablement non amphétaminique, et non dopaminergique des effets induits par des doses modérées de CRL 40476.
3. La dose de 22,5 $mg.kg^{-1}$ apparaît alors comme un équivalent judicieux, chez le macaque rhésus, de ce que devrait être une dose efficace opérationnelle chez l'homme. En effet ses propriétés stimulantes sont indiscutables alors que ses effets résiduels, au niveau de la vigilance, demeurent en dessous des limites de tolérance.
4. Cette dose est donc choisie comme la dose de référence autour de laquelle s'articule les procédures d'évaluation des limites de l'innocuité du CRL 40476.

IV - EVALUATION CHEZ UN PRIMATE DE L'INNOCUITE DU CRL 40476

Les limites de l'innocuité du CRL 40476, ont été déterminées tant sur le plan comportemental que sur le plan végétatif.

Sur le plan végétatif l'étude entreprise sur le macaque rhésus ne fait que compléter et finaliser les données de toxicologie générale recueillies chez les rongeurs et les carnivores. Ainsi les effets du CRL 40476, ont été recherchés à propos des fonctions cardio-respiratoires et des fonctions métaboliques globales dans un cadre général simulant une utilisation opérationnelle.

Sur le plan comportemental les effets du CRL 40476 ont été évalués au niveau de la performance psychomotrice ainsi qu'au niveau de l'émotion. Enfin la toxicité comportementale a été envisagée à propos d'administrations subchroniques de doses élevées.

41 - ETUDE DES EFFETS DU CRL 40476 SUR LES PRINCIPAUX PARAMETRES VEGETATIFS DU MACAQUE RHESUS

- Méthode

Grâce au "Module d'Expérimentation Physiologique sur Primate" (MEPP) développé par le laboratoire, il est possible d'enregistrer, dans un environnement contrôlé, en continu, pendant de longues durées (7 à 15 jours), les principaux paramètres physiologiques de deux macaques rhésus adultes, maintenus assis sur un siège adapté. (13)

Huit sujets sont ainsi soumis à trois séries d'enregistrements continus de 7 jours, recevant au 2°, 3°, 4° et 5° jours soit un placebo (séries pré et post-traitement) soit 22,5 $mg.kg^{-1}$ de CRL 40476 (P.O.) (14).

Les paramètres enregistrés concernent la fréquence cardiaque, l'ECG, la température axillaire, les prises hydriques et alimentaires, les volumes d'excrétats, l'évolution pondérale, l'actographie, le comportement général.

- Résultats

Les données recueillies d'une part, confirment les propriétés stimulantes de la molécule, d'autre part soulignent la discrétion des effets secondaires (14).

Le niveau d'activité générale (mouvements de la tête et des bras) est significativement plus élevé sous traitement dans la première partie de la nuit, alors qu'il redevient normal dans la journée.

Parallèlement à cette augmentation d'activité, il est observé une légère élévation de la fréquence cardiaque et de la température axillaire, plus marquée la nuit que le jour en raison du maintien de l'éveil. Par contre les cycles circadiens ne sont pas modifiés ce qui confirme le caractère limité de l'action du CRL 40476, ainsi que sa spécificité d'action à dose modérée. Enfin les volumes d'échanges hydriques et solides sont maintenus à leur niveau de même que le poids global des sujets. A la dose de 22,5 $mg.kg^{-1}$, équivalent pour le macaque rhésus à la dose opérationnelle potentielle, aucun effet végétatif ne peut constituer une restriction à l'emploi du CRL 40476. Ceci le distingue fondamentalement des amphétaminiques caractérisées par de nombreux effets secondaires aux niveaux cardiaque et métabolique.

42 - ETUDE DE L'INNOCUITE COMPORTEMENTALE DU CRL 40476 CHEZ LE MACAQUE RHESUS

42.1 - EFFET DU CRL 40476 SUR LE COMPORTEMENT SOCIAL DES MACAQUES RHESUS

- Méthode

L'impact du CRL 40476, au niveau de l'émotion est évalué grâce à une épreuve originale, mise au point dans notre laboratoire, le "comportement d'accueil" (15). Cette crise comportementale, facilement quantifiable, apparaît entre deux macaques rhésus qui vivent depuis plus de six mois dans la même cage et que l'on réunit après une séparation d'au moins deux jours. Limitée à deux animaux, cette crise de courte durée, hautement reproductible, peut être multipliée sur un nombre significatif de sujets. Elle permet d'appréhender dans de bonnes conditions méthodologiques l'influence des psychotropes sur les relations sociales des primates.

Dix paires de macaques rhésus adolescents ou subadultes des deux sexes ont été soumises à cette épreuve.

Les observations sous traitement (11,25 - 22,5 et 45 $mg.kg^{-1}$ P.O) sont encadrées d'observations pré et post-traitement sous placebo (16).

- Résultats

En accord avec ce que l'on observe à propos des stimulants classiques, il est constaté une réduction significative du comportement social des macaques rhésus pour les doses 22,5 et 45 $mg.kg^{-1}$ (16).

Les effets sont parallèles dans leur intensité à ceux induits par les doses de 0,1 et 0,25 $mg.kg^{-1}$ de d-amphétamine.

Les résultats obtenus lors d'administration simultanée d'halopéridol écartent l'hypothèse d'un déterminisme dopaminergique. Cette réduction de l'activité sociale pourrait être de nature noradrénergique. Des expériences ultérieures devraient permettre de conclure sur ce point.

Enfin il doit être souligné, qu'aucune réaction pouvant faire suspecter une augmentation d'agressivité n'a été observée.

42.2 - ETUDE DES EFFETS DU CRL 40476 SUR LA PERFORMANCE PSYCHO-MOTRICE DU MACAQUE RHESUS

L'évaluation des effets du CRL 40476, a été conduite, en ce domaine, à propos de deux épreuves classiques de conditionnement opérant : une épreuve dite à intervalle de réponse fixe FI 60 renforcée positivement, une épreuve dite d'échappement, à renforcement négatif.

42.2.1 - **Effets du CRL 40476 sur l'épreuve FI 60**

- Méthode

L'épreuve est fondée sur le principe suivant. Une réponse (appui sur un levier) de l'animal n'est renforcée par un pellet de 0,5 gramme de nourriture que si elle est séparée de la précédente par un délai de 60 secondes. Cette épreuve impliquant un taux de réponse faible devrait être sensible à l'action des stimulants selon la théorie du "rate dependency" de DEWS (17).

Dans ce but, 4 macaques rhésus effectuent cinq épreuves par semaine : quatre sous placebo, une sous traitement. Le CRL 40476 est administré aux doses de 5,7 - 11,25 - 22,5 et 45 $mg.kg^{-1}$ (P.O.) (18).

- Résultats

Compte tenu du caractère relativement court du délai de réponse imposé (60 secondes) il n'est pas possible de mettre en évidence de phénomènes de type augmentation du taux de réponse aussi bien avec le CRL 40476, qu'avec la caféine (7,5 à 30 $mg.kg^{-1}$) ou la d-amphétamine (0,05 à 1 $mg.kg^{-1}$). En fait ces trois substances aux doses considérées, et dans les conditions rapportées, n'entrainent qu'une augmentation significative, et liée à la dose, des phénomènes intermittents d'inhibition constatés dans les épreuves de type FI (18).

L'interprétation précise de cette augmentation des phénomènes d'inhibition ne sera possible qu'après des explorations pharmacologiques complémentaires.

42.2.2 - **Effets du CRL 40476 sur une épreuve d'échappement**

- Méthode

Le principe de cette épreuve consiste à utiliser un son de forte intensité comme renforcement négatif. Son extinction pour une durée d'une minute est provoquée par la réponse de l'animal (appui sur un levier). La mesure des latences de réponse d'un sujet ainsi que le calcul du rapport nombre de réponses / nombre de renforcements permettent d'évaluer la performance de l'animal.

Trois macaques rhésus adultes mâles effectuent 5 épreuves par semaine, 3 sous placebo, la seconde et la quatrième après traitement. La dose de CRL 40476, administrée est la dose de référence 22,5 $mg.kg^{-1}$ (19).

- Résultats

Les propriétés stimulantes de la molécule sont confirmées. Elles se traduisent, classiquement, par une réduction des latences de réponse et par une augmentation du rapport nombre de réponses / nombre de renforcements. Aucun phénomène d'inhibition n'est observé (19).

42.2.3 - **Conclusions**

La mise en jeu d'épreuve de conditionnement opérant a souligné le caractère stimulant général de la molécule, en particulier, à propos de la dose de référence 22,5 $mg.kg^{-1}$ sans permettre toutefois de préciser des limites nouvelles de toxicité comportementale. Par ailleurs aucun trouble de comportement n'a été observé.

42.3 - RECHERCHE CHEZ LE MACAQUE DE PHENOMENES DE TOXICITE COMPORTEMENTALE INDUITS PAR LE CRL 40476

Cette étude a été conduite en deux temps. Dans un premier temps, compte tenu des résultats contradictoires obtenus à propos de la stéréotypie chez les rongeurs, une attention toute particulière a été portée aux animaux recevant des doses élevées de CRL 40476. Les observations ayant conduit à la mise en évidence de phénomènes de stéréotypie, le second temps a pu être abordé. Il visait la recherche de phénomènes de tolérance et éventuellement de dépendance lors d'administrations répétées de doses stéréotypantes de CRL 40476.

42.3.1 - **Mise en évidence chez le macaque de stéréotypies induites par le CRL 40476**

Au cours des expériences relatives à l'actographie nocturne, au comportement social, ou au conditionnement opérant d'éventuels phénomènes de stéréotypie ont été systématiquement recherchés. (8) (16) (18)

- Résultats

Exceptionnellement, chez des sujets très jeunes, des phénomènes de stéréotypies peuvent être observés après administrations répétées de doses égales à 45 $mg.kg^{-1}$ P.O.

Par contre après administration de 60 et 90 $mg.kg^{-1}$ P.O., pratiquement tous les sujets sont soumis à des stéréotypies dont la typologie se distingue de celles induites chez le macaque rhésus par la d-amphétamine ou par l'apomorphine. (20)

42.3.2 - **Recherche de phénomènes de tolérance**

- Méthode

L'évaluation de la tolérance suppose de disposer d'un ou de plusieurs critères précis et sensibles à l'administration de doses élevées de la molécule étudiée. L'existence de stéréotypies chez les primates soumis à des doses élevées de CRL 40476, a déterminé le choix de cet effet comme moyen d'évaluation d'éventuels phénomènes de tolérance, à partir de deux paramètres : latence d'apparition et durée de la crise de stéréotypie. Par ailleurs, il a été convenu d'induire des crises successives jusqu'à l'installation d'une certaine stabilité dans la valeur de ces deux paramètres. Enfin à l'issue de ces administrations successives (19 et 24 jours) une observation minutieuse des sujets visent à la mise en évidence d'éventuels signes de sevrage, ou de sequelles comportementales.

Compte tenu des risques possibles et de la relative rareté des macaques rhésus, cette recherche a été conduite sur une espèce proche du macaque rhésus, le macaque arctoïdes. Quatre femelles de cette espèces ont été soumises pour deux à 15 administrations P.O. de 60 $mg.kg^{-1}$ de CRL 40476 réparties sur 19 jours et pour les deux autres à 15 administrations P.O. de CRL 40476, réparties sur 24 jours. (20)

- Résultats

L'analyse des résultats obtenus a conduit aux conclusions suivantes (20) :

1. Aux doses de 60 et 90 $mg.kg^{-1}$ le CRL 40476 induit, chez le macaque, des comportements stéréotypés.
2. Les comportements stéréotypés ne peuvent être superposés aux stéréotypies amphétaminiques. En particulier, l'atteinte des sujets apparaît comme moins profonde.
3. Un phénomène de tolérance a été observé, au cours des crises de stéréotypie, son caractère limité ne permet pas de l'assimiler à l'accoutumance amphétaminique.
4. L'absence de sequelles comportementales et en particulier de syndrome de sevrage exclut, dans les conditions d'expérience, l'existence d'un phénomène de dépendance.

44 - CONCLUSIONS

L'ensemble des expériences conduites chez le macaque rhésus et visant au contrôle de l'innocuité comportementale et végétative du CRL 40476 conduit aux conclusions suivantes :

- A la dose utile de 22.5 $mg.kg^{-1}$ aucun trouble réel de nature végétative ou comportementale n'a été mis en évidence. Tous les effets observés demeurent dans les limites de ceux que l'on peut prévoir à propos d'un stimulant. (21)
  Aucun effet de type amphétaminique n'est mis en évidence en particulier dans la composante dopaminergique.
- Aux doses élevées, triples ou quadruples de la dose utile, apparaissent des signes évidents de stimulation dopaminergique. Cependant l'étude de la tolérance, et celle de la nature des stéréotypies, après administrations élevées et répétées de CRL 40476 chez le primate, distinguent les effets dus à cette substance de ceux de l'amphétamine.
  Enfin aucun phénomène de dépendance n'a été mis en évidence au cours de ces études.

V - CONCLUSIONS GENERALES

La recherche des limites d'efficacité et d'innocuité du CRL 40476 a été conduite de la manière la plus extensive possible, sur un modèle primate reconnu comme un succédané de l'homme particulièrement efficace en matière de vigilance, le macaque rhésus. L'ensemble de la recherche a été articulé autour d'une dose équivalente à celles susceptibles d'induire chez l'homme une vigilance nocturne compatible avec des tâches opérationnelles.

Globalement le CRL 40476 s'est révélé, à la dose équivalente déterminée, comme possédant des propriétés éveillantes et stimulantes générales au moins équivalentes à celles de la d-amphétamine mais sans en présenter les effets secondaires végétatifs ou comportementaux.

De manière plus précise il doit être souligné que les effets éveillants, particulièrement puissants, du CRL 40476, sont obtenus sans désorganisation de la vigilance diurne, sans effet rebond véritable, accompagnés seulement d'un effet de récupération très limité dans son intensité et dans sa durée.

De même l'absence de toute propriété anorexigène, la limitation des perturbations végétatives à une légère augmentation de la fréquence cardiaque nocturne, reflet de l'insomnie, ainsi que le respect de l'intégrité de cycles circadiens tels que ceux de la fréquence cardiaque ou de la température corporelle constituent des traits tout à fait remarquables en regard de la puissance des effets éveillants.

Enfin la recherche de l'efficacité et de l'innocuité comportementale lors d'épreuves de conditionnement opérant, ou lors d'observation du comportement social, ne met en évidence que des effets de type stimulant de nature identique à ceux induits par de doses faibles d'amphétamine ou de doses élevées de caféine. Aucune perturbation comportementale n'a pu être mise en évidence, en particulier, dans le domaine de la dépendance. Les phénomènes de tolérance demeurent limités dans leur intensité et dans le temps. Ils ne peuvent être comparés à l'évolution de la tolérance amphétaminique.

A ce stade de la recherche deux axes de développement doivent être envisagés.

Le premier, de caractère fondamental, vise à l'approfondissement chez l'animal, des mécanismes pharmacologiques sous-tendant les effets stimulants observés. En particulier, il s'agirait de confirmer, chez le macaque rhésus, l'existence d'effets de type alpha adrénergiques, aux doses efficaces, distincts d'effets dopaminergiques caractéristiques de doses plus élevées.

Le second axe de développement a pour objectif de préciser les conditions d'utilisation du CRL 40476 comme stimulant opérationnel. Une première étape, indispensable, consiste dans la définition précise des doses et fréquences d'administration, chez l'homme sain, du CRL 40476. Cette étape ne peut-être conduite qu'en milieu hospitalo-universitaire, pour des raisons évidentes de sécurité. Son aboutissement permettra d'envisager par la suite des expérimentations en milieu militaire dans des conditions progressivement de plus en plus proches de la réalité opérationnelle.

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REMERCIEMENTS

Cette recherche a été réalisée avec le soutien financier de la Direction des Recherches Etudes et Techniques, PARIS.

Les auteurs remercient MM ANTON G., BARRAULT B., BLOSTIN R., SINTACHE G. et Mmes CHABAS S. et LAROUSSERIE J. pour leur collaboration.

Pharmacological Approaches to Performance Enhancement in Animals

by
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SUMMARY

Drug effects were studied on learning and working memory performance in young, normal rats, as well as on reactions to hypoxia and stress. While some of the treatments reduced cognitive parameters under normal conditions, none improved them in a meaningful way. However, several substances were found to improve performance disrupted by exposure to hypoxia. These substances included piracetam, nimodipine, and ipsapirone (TVX Q 7021). An additional characteristic of ipsapirone was an amelioration of negative responses to stress. Due to the well-understood mechanisms of action of nimodipine and ipsapirone, their low toxicity, and their lack of negative effects on normal cognitive performance, it is suggested that these drugs could prove to be useful therapeutic agents under conditions of high information processing load.

INTRODUCTION

Performance in general can be split into cognitive and non-cognitive elements, the former comprising attention, learning and memory, and the latter including arousal, motivation and motor response parameters. The cognitive elements thus lie at the heart of information processing and decision making, whereas the non-cognitive elements influence the selection of data for processing and the manner or intensity of response production. If substances are desired that facilitate information processing, then the behaviors to be measured must be complex enough to allow a separation of the cognitive and non-cognitive elements influencing performance. This is particularly true in the case of psychopharmacological research with animals, since verbal responses cannot be obtained.

Two very important aspects of information processing are the formation of associations between stimuli or between stimuli and responses (learning) and the storage and retrieval of such associations (memory) for future situations. Accordingly, in order to find out whether drugs can positively influence cognitive elements associated with task performance, the effects of such drugs should be measured in behavioral situations explicitly requiring learning and memory. While memory, particularly of the short-term or "working" variety, can be empirically defined and studied as a more-or-less isolated construct, the study of learning is a bit more complex. This is due to the fact that in order to study the change in behavior that signals learning, moment-to-moment storage and retrieval of information (memory) must also occur. One can conclude from this information that a good way to discover how a drug affects performance is to obtain separable or independent measures of drug effects on learning, memory, and the non-cognitive elements.

The separation of cognitive and non-cognitive elements affecting performance in a particular task can be achieved by requiring the selection of one response from a group of alternative responses. Given the prevailing response contingencies of reward or punishment, the accuracy of cognitive operations can be assessed by the appropriateness of response selection. Alternatively, the status of non-cognitive elements can be assessed by the absolute number of emitted responses and the speed with which they were made. Behavioral procedures in which only changes in the rate of a single response type can be measured can therefore not easily provide separate estimates of treatment effects on cognitive and non-cognitive aspects of performance. Procedures of this type include passive avoidance conditioning as well as those in which free-operant schedules of reinforcement on a single manipulandum are employed. Thus, although treatment effects on performance can be evaluated in these latter test systems, it can often not be determined whether such effects were produced through important or trivial means.

Two main ways that drugs can usefully improve performance are to either facilitate cognitive processing under normal conditions or to relieve the negative effects of some disruptive condition. In aerospace situations, two such negative conditions are hypoxia and stress. In accordance with these ideas, we have studied the effects of a wide range of drugs on 1) learning and memory in young normal rats, and 2) performance deficits in young rats resulting from hypoxia and stress. The drugs chosen for study were anxiolytics, psychostimulants, cholinergic agonists, calcium channel antagonists, and a heterogenous group of "cognition enhancing" compounds with unknown mechanisms of action. This latter group of drugs consisted primarily of hydergine and the nootropic compounds piracetam and pramiracetam.

The tasks chosen for the assessment of learning and memory were selected on the basis of the theoretical considerations outlined above: multiple response alternatives, allowing separable estimation of cognitive and non-cognitive aspects of behavior. For the study of learning, a repeated acquisition task was used in which well-trained animals daily solved a labyrinth problem. Although the general nature of the problem was the same from day to day, the specific solution varied across sessions.

This allowed a stable baseline of learning errors upon which to measure drug effects. The eight-arm radial maze (Olton and Samuelson, 1976) was selected for the assessment of working memory.

The effects of hypoxia and stress on behavior are quite marked and not limited to one particular cognitive or non-cognitive aspect of behavior. Regarding hypoxia, drugs were assessed for antagonism of hypoxia-induced "amnesia" of the passive avoidance response. Regarding stress, drugs were evaluated for inhibition of stress-induced maladaptive responses in conflict and social settings.

METHODS

Working memory assessment in the eight-arm radial maze. Male albino Wistar rats served as subjects, and were 180-200 g upon receipt, eventually stabilized to 250-350 g through food deprivation. Training took place in a computer-operated 8-arm radial maze, with a shape and dimensions similar to those described by Olton and Samuelson (1976). The maze was fixed to an elevated table and was shaped like a wagon-wheel with a hub from which 8 arms radiated. Each arm had floor and walls made of black plastic and a hinged ceiling made of clear plastic. The maze center (hub) was also covered with a clear plastic lid, which could be totally removed by lifting the knob on top. Guillotine doors were situated at the point where each arm joined the hub, and were connected to tubes with high air pressure. Computer-controlled switches were located under the table surface, and determined whether air pressure opened or closed the doors. Each arm also contained two microswitches in the floor; one near the entry door and one near the end of the arm. A small metal cup was at the end of each arm which held the food pellet reinforcement. The two microswitches in each arm and the switches controlling the guillotine doors were connected via an LVB microcomputer interface (MED Associates, Inc., Box 47, East Fairfield, VT, USA) to a TRS-80 Model III microcomputer (Tandy). The microcomputer controlled the experimental session and recorded the data.

After one week adaptation time and a short pretraining phase, the actual training phase was begun. During this period and extending into the test phase, rats received food only during the sessions and an additional supplement of 12 g shortly thereafter. Each training session was performed automatically by the computer after each of the eight arms had been baited with a piece of food at the end. Rats were placed singly in the maze center at the start of the session while all guillotine doors were closed. The session was started by opening all doors simultaneously; after the eighth arm selection (activation of a microswitch at the end of an arm) or the passage of 10 min, the session was ended by closing all doors. After about ten sessions, rats began to reduce the number of repeated entries into arms which had already been visited (food taken and eaten) and to visit only the remaining arms. An error in this task was defined as a repeated arm visit, and at the end of this training phase, rats made 0-1 errors per session (7-8 correct arm choices out of 8).

The drug test phase began after stable performance was attained in about 20 rats. Two sorts of drug tests were performed. First, drugs were tested for amnestic effects by injecting the subjects shortly before a session conducted as described above. Drug tests were separated by at least 2 control sessions, in which animals were pretreated with normal saline. Second, drugs were tested for positive effects on working memory. In this type of drug test, a 1- or 4-hour interval was imposed between the fifth and the sixth arm choice. Rats were removed from the maze during this delay, which had the effect of reducing arm choice accuracy on the last two choices. Test drugs were injected during the delay on test sessions; at least 2 saline control sessions were again interpolated between drug test sessions.

Learning assessment in the water labyrinth. Rats of the same strain and weight upon reception as described in the preceding section were used. Subjects were allowed access to food and water ad-libitum throughout the experiments. Sessions were executed in a water labyrinth tank that was made out of gray plastic and was approximately 1 m long by 50 cm wide by 50 cm tall. Before each session, the tank was filled half-way with cold (15°C) water. After two initial practice sessions in a shortened form of the maze shown in Fig. 1, male rats were given three swimming trials per day. Each trial consisted of placement of the rat at the point marked "S". The subject then had to swim to the point marked "F" in order to find the escape ladder. Barriers were also present at either the points marked with an "a" or those marked with a "b", so that the rat was forced to turn either always left or always right at points "1" and "2". During each session, two parameters were measured: swimming time and the number of directional turning errors made. The first acquisition phase consisted of a series of across-session reversals, where the correct turning direction alternated over sessions but was constant over the three trials within a session. When turning errors were markedly reduced, the within-session reversal phase was begun. Each rat now received four trials per session: the first two were always with one correct turning direction and the last two were with always with the opposite direction. The rats first received a number of sessions where, for instance, right turns were initially correct. Following performance improvement, the situation was reversed and the subjects received a number of consecutive sessions in which left turns were initially correct. The last training phase consisted of using a semi-random sequence of correct starting direction over sessions. Daily saline injection was also begun at this time so that drug testing could take place as soon as the number of total turning errors per session stabilized. At asymptote, 12-15 errors per session were the average. Test drugs or saline were injected shortly before each session, and test animals were split into vehicle and drug

groups on each test day, formed in order to control for the previous day's performance. This then allowed between-group comparisons, shown below in the results section.

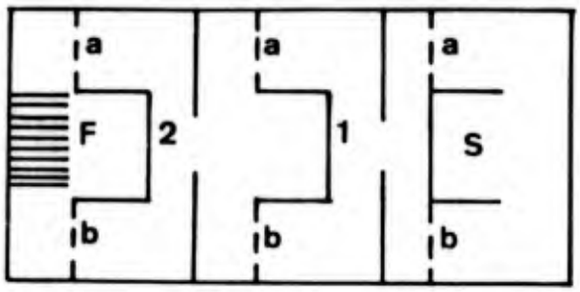

Fig. 1. Diagram of the water labyrinth used to assess learning in a repeated acquisition procedure, as seen from above.

Hypoxia-induced amnesia in the passive avoidance task. Drugs were tested for antagonism of hypoxia-induced retrograde amnesia in a passive avoidance procedure similar to that described in Hoffmeister et al. (1982). Briefly, male Sprague-Dawley rats were placed individually into the bright side of a two-chamber box. Due to pre-existing tendancies, rats quickly entered the dark chamber, whereupon the connecting door was closed and a small foot shock (2 mA for 2 sec, repeated 4 times with an intershock interval of 10 sec) was delivered. Immediately thereafter, rats were placed in an air-tight chamber which was perfused with a gas mixture of 3.8% oxygen and 96.2% nitrogen. Rats remained under these conditions until either they exhibited a gasping response or 400 sec had passed. Four hours later, rats were replaced in the bright chamber. The door between the two chambers was opened and the time required before rats entered the dark compartment (to a maximum of 3 min) was measured. For each drug test, three groups of 15 rats each were used: one which received test drug vehicle (control treatment) and no hypoxia, one receiving vehicle and hypoxia, and one receiving test drug and hypoxia. Footshock under these conditions always resulted in a long latency to enter the dark compartment and the hypoxic treatment reversed the shock effect, thus resulting in a shorter latency to enter the dark compartment. The difference in entry latency between the vehicle-treated no-hypoxia group and the vehicle-treated hypoxia group was set to 100% and the extent to which drug treatment affected behavior of hypoxia treated rats was expressed as percent antagonism of the hypoxic effect.

Stress assessment: the shock-suppressed drinking test. Male Wistar rats were housed for an adaptation period of 10 days after delivery and given free access to food and water. One day before the experimental session, water was removed. Drugs (depending on pharmacokinetic properties and injection route) were injected 30-60 min before the session. At the beginning of the test session, rats were placed singly into clear plastic cages with wire mesh lids. A drinking tube connected to a water-filled bottle was inserted through the lid, and was connected to an electronic shocker and lick-response counter. Rats were allowed to drink during the following 15 min, but every twentieth lick was followed by a 0.8 mA, 50 Hz shock that lasted as long as the rat's tongue was in contact with the tube. Relative to such a procedure in which licking was not so punished, the delivery of shocks suppressed drinking in water-deprived rats. The data were expressed in terms of average number of shocks accepted per rat, and 8 rats were used per treatment condition.

Stress assessment: defensive behavior in defeated rats. Male, group-housed Wistar rats were kept on a reversed day-night cycle and given free access to food and water. On the first experimental session, rats were placed singly into the large home cage (80x60x50 cm) of a genetically aggressive male TMD-S3 rat; the normally resident female TMD-S3 rat was previously removed. For the first five min of the session, the male TMD-S3 rat was enclosed in a small (19x14x14 cm) wire mesh cage within the larger home cage, and the frequency and duration of various exploratory behaviors in the Wistar intruder rat were measured. Behavioral assessment was performed using a continuous rating method: a well-trained experimenter continuously assigned the ongoing behavior of the intruder rat into one of nine categories and entered this information into a microcomputer, which was programmed to deliver a summary of behavior durations at the end of the session. At the end of this initial 5-min period, the experimenter released the resident TMD-S3 rat and allowed the two rats to interact until the resident rat defeated the intruder. Defeat was defined as the adaptation of a full submissive posture by the intruder rat. This procedure was repeated in the next session 24 hours later, with the exceptions that 1) only the initial 5-min period occurred, and 2) intruder rats were injected with either the test drug or drug vehicle i.p. 30 min before the session. Six Wistar rats were studied per treatment condition. The total duration of defensive behavior was calculated for the purposes of data analysis, which was made up of the following behavioral elements: defensive upright posture, freezing, fleeing, and submissive posture. Freezing formed the vast majority of the defensive behavior observed in the second session.

RESULTS

Working memory assessment in the eight-arm radial maze. The effects of various drugs on performance in the 8-arm radial maze are shown in Table 1. Diazepam, ipsapirone and scopolamine were tested for amnestic effects in the no-delay form of the task, while all other drugs were tested on the delayed form. Diazepam reduced response accuracy at several doses, and did so significantly at 5 mg/kg. Similar results were found for the muscarinic cholinergic antagonist scopolamine, which reduced accuracy significantly at 0.5 mg/kg. Ipsapirone, however, had no such amnestic effects at doses up to 20 mg/kg. Of the cholinergic agonists tested in the delayed task form (RS-86, oxotremorine, arecoline, physostigmine, and nicotine), RS-86 and physostigmine produced positive effects that did not, however, reach statistical significance. Positive effects were found neither for the nootropic compound pramiracetam nor for hydergine, a drug used clinically to improve cognition in the elderly. The calcium channel antagonist nimodipine and the potassium channel agonist 4-aminopyridine were also without effect.

Table 1.
Effects of Test Drugs on Rat Working Memory Accuracy in the 8-Arm Radial Maze.

Substance[1]	Dose (mg/kg)	N[2]	% Control Arm Choice Accuracy: Choices 5-8 on No-Delay Test	% Control Arm Choice Accuracy: Post-Delay on Delay Test
Diazepam	1.25	5	91	
	2.5	5	101	
	5	4	60*	
	10	4	79	
	20	7	80	
Ipsapirone	5	6	91	
	10	11	91	
	20	5	98	
Scopolamine	0.05	4	72	
	0.5	5	65*	
RS-86	0.32	20		110
	0.64	20		133
Oxotremorine	0.08	20		97
Arecoline	1.25	20		104
Physostigmine	0.08	20		119
	0.16	20		109
	0.32	20		79
Nicotine	0.16	20		100
	0.32	20		88
	0.64	20		103
Pramiracetam	2.5	20		85
Hydergine	20	20		94
Nimodipine	1	20		109
	10	20		96
4-Aminopyridine	0.64	20		103

[1] All drugs were given i.p., except for nimodipine and hydergine which were given p.o.

[2] Number of subjects tested.

* Statistically significant difference from control by paired t-test at $p < 0.05$.

Learning assessment in the water labyrinth. Drug effects on repeated acquisition performance are shown separately on trial errors and on swimming time in Table 2. Diazepam at 5 mg/kg and scopolamine at both 0.25 and 0.5 mg/kg significantly increased the number of errors made during learning, but only the higher dose of scopolamine also correspondingly increased swimming time. Methylscopolamine did not share the effects of scopolamine, however. Ipsapirone had no significant effect on performance, but did slightly reduce the time required to navigate the maze. Amphetamine slightly reduced errors at 0.5 mg/kg, but had the opposite effect at 1 mg/kg, a dose which also increased swimming time somewhat. The cholinergic agonists RS-86, oxotremorine,

arecoline and physostigmine were never found to improve either learning (in terms of reducing errors) or swimming speed. Indeed, significant negative effects were found at high doses: 1.25 mg/kg RS-86 increased only swimming time, while 0.2 mg/kg physostigmine increased both errors and swimming time. The nootropics piracetam and pramiracetam were without effect, as were hydergine, nimodipine and 4-aminopyridine, while the highest doses of 3,4-diaminopyridine significantly increased errors.

Table 2.
Effects of Test Drugs on Rat Performance in a Water Labyrinth Repeated Acquisition Task.

Substance[1]	Dose (mg/kg)	N[2]	% Control Errors	% Control Swimming Time
Diazepam	5	15	121*	117
Ipsapirone	5	15	107	79
	10	10	100	86
d,l-Amphetamine	0.5	15	87	101
	1	12	121	124
Scopolamine	0.25	15	150*	107*
	0.5	11	143*	145*
Methylscopolamine	0.5	12	100	100
RS-86	0.25	12	107	104
	0.5	9	156	143*
	1.25	15	114	147*
Oxotremorine	0.1	15	100	88
Arecoline	1	10	118	114
Physostigmine	0.1	9	92	94
	0.16	9	117*	116*
	0.2	9	320*	951*
Piracetam	100	12	114	105
	200	10	108	95
Pramiracetam	1	22	92	95
	5	22	108	108
	10	11	100	102
Hydergine	10	9	118	103
Nimodipine	10	9	100	95
4-Aminopyridine	1	9	106	99
3,4-Diaminopyridine	1	10	107*	100
	5	9	191*	132

[1] All drugs were given i.p., except for hydergine which was given p.o.

[2] Number of subjects tested.

* Statistically significant difference from control by paired t-test at $p < 0.05$.

Hypoxia-induced amnesia in the passive avoidance task. Table 3 lists the effects of various drugs on the hypoxia-induced deficit in rat passive avoidance performance. Crossover latency is shown for each treatment condition for both rats given control treatment (vehicle) and no hypoxia and those given vehicle and hypoxia, so that the magnitude of the hypoxic effect is apparent. Diazepam and ipsapirone, as well as piracetam, vincamine (another drug marketed for the treatment of age-related cognitive impairment), and nimodipine significantly and virtually completely antagonized the hypoxic effect. Hydergine also had antagonistic effects and while they did not reach statistical significance, they were consistent across the three highest doses, indicating their probable reliability. Amphetamine, on the other hand tended to increase the hypoxic effect.

Table 3.
Effects of Test Substances on Hypoxia-Induced Passive Avoidance Deficits in the Rat.

Substance[1]	Dose (mg/kg)	Entrance Latency (sec) in Vehicle Control		% Antagonism of Hypoxic Effect
		No Hypoxia	Hypoxia	
Diazepam	0.01	162	94	26
	0.1	162	94	57
	1	162	94	73*
	10	167	101	85*
Ipsapirone	0.001	171	104	49*
	0.01	171	104	71*
	0.1	171	104	62*
	1	171	104	84*
	10	172	96	103*
d-Amphetamine	3	145	114	-53
Piracetam	0.1	162	94	45
	3	162	94	58*
	30	167	101	81*
	300	167	101	80*
Hydergine	0.03	167	101	19
	0.3	163	92	69
	3	163	92	58
	30	163	92	64
Vincamine	0.001	167	101	15
	0.01	167	101	43
	0.1	163	92	58*
	1	163	92	96*
Nimodipine	0.3	176	116	49*
	0.6	176	116	65*
	1	176	116	79

[1] All drugs were given p.o., except for nimodipine which was given i.p.

* Statistically significant difference from vehicle-treated hypoxia controls in a grouped t-test at $p < 0.05$.

Stress assessment: the shock-suppressed drinking test. The effects of diazepam, as a clinically effective anxiolytic drug, and ipsapirone, as a representative of a novel serotonergic class of putative anxiolytics, were compared in the shock-suppressed drinking test (Table 4). Both compounds significantly increased the number of shocks accepted, and thus increased the amount of water consumed. The absolute magnitude of the diazepam effect appeared to be larger than that of the ipsapirone effect, however.

Table 4.
Effects of Diazepam and Ipsapirone on Rat Stress Response in the Shock-Suppressed Drinking Test.

Substance[1]	Dose (mg/kg)	Mean Number of Shocks Accepted over 15 min
Diazepam	Vehicle Control	2.3
	1.25	15.5*
	2.5	15.9*
	5	47.5*
Ipsapirone	Vehicle Control	2.8
	1.25	3.4
	5	4.1
	10	5.0*

[1] Both drugs were injected i.p. and 8 animals were tested in each treatment condition.

* Statistically significant difference from vehicle control by Mann-Whitney U-test at $p < 0.05$.

Stress assessment: defensive behavior in defeated rats. Diazepam and ipsapirone were again compared for their anti-stress effects in the defeated rat test. Diazepam from 1 to 5 mg/kg produced only slight increases in the amount of defensive behaviors shown by the intruder rats. Conversely, ipsapirone at 2.5 mg/kg significantly reduced this behavioral parameter, simultaneously increasing the occurrence of normal exploratory behaviors.

Table 5.
Effects of Diazepam and Ipsapirone on the Defensive Behavior of Previously Defeated Rats.

Substance[1]	Dose (mg/kg)	N[2]	Mean Duration (sec) of Defensive Behavior per 5-min Session		% Change
			Vehicle	Test Drug	
Diazepam	1	10	123	140	+ 14
	2	10	89	92	+ 3
	3	7	118	134	+ 14
	5	10	143	174	+ 22
Ipsapirone	2.5	10	152	95	- 37*

[1]Both drugs were injected i.p.

[2]Number of vehicle- and drug-treated pairs of animals.

*Statistically significant difference from vehicle control in a Mann-Whitney U-test at $p < 0.05$.

DISCUSSION

The present research report began with an assessment of the effects on learning and working memory under normal conditions of a group of drugs reported at various times to have specific positive or negative effects on these cognitive parameters. We will therefore begin the discussion by considering these effects by substance class.

Drug effects on learning and memory. In the eight-arm radial maze and water labyrinth experiments, diazepam was found to have significant negative effects on learning and memory at doses leaving motor performance intact. Benzodiazepine anxiolytics such as diazepam have frequently been reported to have such negative cognitive effects (see Thiébot, 1985 for review). For example, Hughes et al. (1984) showed that chronic administration of diazepam persistently disrupted the acquisition of color and line-shape discriminations in pigeons. Chlordiazepoxide was shown to disrupt performance in a delayed pair comparison (short-term memory) task, with the greatest effects seen at the shortest memory intervals (Sahgal and Iversen, 1978). This effect was hypothesized to be on the encoding stage of memory; that is, the transfer of information from perception to memory storage. That such negative effects generalize to the clinical situation with humans is well known, and has been reported by Loke et al. (1985), among others. The barbiturate anxiolytics have also been implicated in cognitive disruption. Sahgal et al. (1980) reported that amylobarbitone reduced performance in a delayed stimulus comparison task in a way which indicated a disturbance in acquisition (encoding) of information.

Thus, although benzodiazepine and barbiturate drugs are effective in reducing anxiety and some signs of stress, a price is paid in terms of information processing capacity. These substances produce their effects through interaction with receptor and transduction systems for the inhibitory neurotransmitter gamma-amino-butyric acid (GABA) in the brain (e.g., Paul et al., 1981). In the search for anxiolytic drugs lacking this mechanism of action, ipsapirone (TVX Q 7821) was discovered. Ipsapirone does not directly affect GABA neurotransmission; rather, it appears to selectively interact with a sub-type of serotonin receptors known as 5-HT1A receptors (Glaser and Traber, 1985; Glaser et al., 1985). Ipsapirone nonetheless shares with benzodiazepines such as diazepam activity in a number of animal models of anxiety (Traber et al., 1984). In the present experiments, however, ipsapirone lacked the negative effects of diazepam on learning and memory. The effects of ipsapirone on stress will be discussed below.

Amphetamine's effects on learning were examined because some reports do exist in the literature that psychostimulants such as amphetamine can reduce the occurrence of errors during learning (e.g., repeated discrimination reversals: Calhoun and Jones, 1974; Handley and Calhoun, 1978; repeated acquisition of response chains: Harting and McMillan, 1976). In the present repeated route (response) reversal task, though, no such positive effects were seen. These results are in agreement with the bulk of repeated acquisition reports, indicating that low doses of amphetamine have no measurable specific effects on learning rate and that high doses can disrupt performance (e.g., Thompson, 1973; Moerschbaecher et al., 1979; Howard and Pollard, 1983).

Drugs interacting with acetylcholine receptors (AChR) in the brain have a long history of study. Muscarinic AChR antagonists like scopolamine have well-documented negative effects on behaviors requiring learning and memory, while forms of these agents that do not cross the blood-brain barrier lack such cognitive effects (see Spencer and Lal, 1983 for review). Similarly, in the present study, scopolamine, but not the peripherally-restricted form methylscopolamine, significantly reduced both learning and memory performance. However, although negative effects were found for the muscarinic AChR antagonist scopolamine, positive effects were not found for the directly-acting agonists RS-86, oxotremorine, and arecoline, or for the indirectly-acting agonist physostigmine.

It has indeed proven difficult in the past to find positive selective effects of cholinergic agonists on normal cognitive functions. Although reports of performance improvement exist for retention of the passive avoidance response (e.g., Flood et al., 1981; Flood et al., 1985; Haroutunian et al., 1985), very few positive findings have been reported using more complex and much more selective procedures such as discrimination retention and delayed discriminative response (Stanes et al., 1976; Bartus et al., 1983). In fact, studies citing no or negative effects of cholinergic agonists on learning (Howard and Pollard, 1983; Penetar, 1985) and memory (delayed discriminative response: Heise and Hudson, 1985a; delayed conditional discrimination: Penetar and McDonough, 1983; Heise and Hudson, 1985b) have dominated. A similar state of affairs seems to pertain to nicotine, an agonist at nicotinic AChR in the brain and periphery. Although nicotine can increase passive avoidance performance (Nordberg and Bergh, 1985), nicotine did not positively influence memory performance in the eight-arm radial maze in the present study. The information available to date suggests that physostigmine is still the most cognitively active compound known in the cholinergic agonist substance group, and that positive effects are weak but tend more toward memory than learning facilitation.

The nootropics are a group of structurally similar compounds with piracetam as prototype. These substances include aniracetam, oxiracetam, etiracetam, and pramiracetam, and are primarily known for their positive effects against hypoxia and other acute disruptive treatments (see Nicolaus, 1982, for review). These substances have extremely low toxicity, very subtle behavioral effects, and an as yet unclear mechanism of action. In the normal animal, nootropic drugs have been reported to enhance passive avoidance behavior (Yamada et al., 1985) and to marginally but significantly improve memory performance in animals trained on delayed discriminative response (Bartus et al., 1983; Poschel et al., 1983; Pontecorvo and Evans, 1985). In the present study, no positive effect of pramiracetam on memory performance in the eight-arm radial maze was seen, and neither piracetam nor pramiracetam improved learning performance. Hydergine, although not structurally related to the nootropics, has a similar pattern of pharmacological effects and was also without activity in the present learning and memory experiments.

Drugs that bind with receptors to influence the flow of specific ions through their membrane channels have also been hypothesized to have useful effects on information processing. The aminopyridines are compounds long studied in electrophysiological settings for their activity in increasing cellular depolarization and neurotransmitter release, apparently accomplished through a blockade of potassium channels and perhaps a related enhancement of calcium ion influx (Matsumoto and Riker, 1984). We have tested some of these compounds due to reports that age-related behavioral deficits could be favorably influenced (e.g., Peterson and Gibson, 1983). In the current learning and memory experiments, however, both 4-aminopyridine and 3,4-diaminopyridine were without positive effect. Nimodipine is a representative of the dihydropyridine class of calcium channel antagonists, with pharmacological effects in animals indicating central nervous system activity (Hoffmeister et al., 1982). Nimodipine did not influence the course of normal learning and memory in the present study, however.

Drug effects on behavioral deficits induced by hypoxia and stress. In agreement with previous research (e.g., Schindler et al., 1984), piracetam antagonized the passive avoidance deficit induced in rats by hypoxia, as did the geriatric drugs hydergine and vincamine. Diazepam and the putative anxiolytic ipsapirone were also active and these effects may have been related to a calming influence, especially when the negative effects of amphetamine in this model are considered. In this connection, however, it must be remembered that while diazepam had somewhat sedating effects on swimming in the water maze, ipsapirone actually increased swimming speed slightly. This means that while sedative compounds can antagonize hypoxic effects, a compound must not be sedative in order to be anti-hypoxic, a consideration that also holds for the nootropic drugs.

Nimodipine displayed anti-hypoxic effects, as noted by Hoffmeister et al. (1982), who also found that nimodipine significantly increased the survival time of mice exposed to a hypoxic atmosphere. That these effects of nimodipine are likely to be due to a protective neuronal action via calcium channel blockade is indicated by studies on another form of neurocellular anoxia, brain ischemia. During ischemic attacks, calcium ions enter nerve cells and appear to at least partially provoke cell death through a variety of cellular mechanisms (Dienel, 1984; Sakamoto et al., 1986). Treatment with nimodipine has been shown in a number of species to improve brain morphological and neurological outcome (Steen et al., 1983; Steen et al., 1985; Meyer et al., 1986). An additional and probably related property of nimodipine is its ability to improve response to traumatic shock (Lefer and Carrow, 1981).

The study of drug effects on stress is complicated by the problems of how to define stress and how to regard the animal's reaction to stress. Stress is considered here, somewhat circularly, to result when an organism is exposed to aversive circumstances. An organism can respond either adaptively or maladaptively to such stress. For the current purposes, a maladaptive response to stress is considered to be a response that brings no direct benefit to the organism, but competes with the production of other, more beneficial responses. In the first stress model considered, water deprived rats were given a non-damaging shock to the tongue contingent on drinking. The cessation of drinking could be considered a maladaptive response to shock induced stress in this case, particularly if prolonged; both diazepam and ipsapirone inhibited this response to stress and accordingly increased drinking. The second model was the defeated rat procedure, which might be considered a more appropriate model of stress on naturalistic grounds. In this case, the intruder rat's response to previous defeat is primarily to engage in freezing behavior in the presence of the restrained resident rat. One could consider such a freezing response maladaptive, considering that the intruder rat is in no present danger. Ipsapirone reduced the amount of time such rats engaged in defensive behavior, but diazepam had, if anything, opposite effects. Based on these results, ipsapirone would appear to have salutary effects on reaction to stress across situations.

CONCLUSIONS

In aerospace applications, desirable drug effects would be to increase information processing and/or reaction time parameters under normal conditions as well as to decrease the negative effects influences such as hypoxia and stress can have on performance. The representative results of the first two experiments illustrated that none of the currently tested drugs can consistently improve normal cognitive processing in a meaningful way. On the other hand, the latter three experiments were intended to show that pharmacological intervention could be successful in offsetting the disruptive sequelae of hypoxia and stress. Further points in the treatment of these phenomena, however, are that it is important to use compounds which 1) do not themselves negatively affect cognitive processing, such as classical anxiolytic agents, and 2) are well understood from a neurobiological point of view. Two therapeutic agents that meet these conditions are nimodipine and ipsapirone.

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Discussion

Price, US

Actually, I had already talked with Dr. Banderet about the paper on looking at tyrosine in the chamber runs and I simply wanted to make the point I guess, that in doing such work one needs to try and look at the effects of nicotine and if Dr. Wurtman is still here perhaps he can comment on the effects of nicotine on norepinephrine and tyrosine because if you are doing human studies one needs to be able to control for that, I think. Particularly when you are measuring performance with tools which measure mood and vigilance and those kinds of things. Is Dr. Wurtman still here? Maybe someone else could comment on it then. Matter of clarification. I just say that if you do a 4-hour chamber run, certainly you are going to have nicotine withdrawal effects. Maybe some of us have experienced that here during the talks. But, the results on nicotine itself as a stimulant are somewhat mixed but nicotine withdrawal effects are very clear in the literature and that's the reason I bring it up.

L'EVALUATION DE LA VIGILANCE DANS LES ETUDES DE PHARMACOLOGIE EN AERONAUTIQUE.

par

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RESUME

Pendant de longues années, l'activité aérienne a paru, pour les médecins du personnel navigant, incompatible avec toute prise médicamenteuse. Aujourd'hui il apparait que le personnel navigant doit pouvoir bénéficier de la pharmacologie moderne tout en poursuivant sa mission dans tous les cas où la sécurité du vol n'est pas mise en jeu.

Cependant, à tout moment, ce personnel doit garder un niveau élevé de vigilance et éviter toute diminution des performances intellectuelles. Les drogues utilisées par les médecins de l'aéronautique doivent être choisies à ce propos sur des critères objectifs.

Ainsi,que ce soit pour juger de l'efficacité des molécules psychostimulantes sur un opérateur humain en situation ou pour évaluer les effets secondaires centraux d'une molécule utilisée dans un tout autre domaine thérapeutique, il est nécessaire de disposer d'un moyen suffisamment précis pour rendre compte des modifications de la performance psychique et du maintien d'un niveau donné de vigilance.

Cette évaluation de la performance, qui dépend du niveau d'attention, n'est pas chose aisée, surtout s'il s'agit de la mesurer dans un milieu aussi spécifique que l'aéronautique où à la complexité de la tâche de travail s'ajoute bien souvent une contrainte de l'environnement.

Pour ce faire, le Laboratoire de Médecine Aérospatiale a mis au point ou adapté au contexte aéronautique un certain nombre de tests permettant d'étudier deux domaines particuliers de la vigilance : psychomotricité et mémorisation.

Du point de vue ergonomique, la performance est définie comme la capacité à accomplir une tâche simple ou complexe en un temps limité, le plus court possible et avec le minimum d'erreurs ou d'omissions.

Elle est caractérisée par deux paramètres : le temps d'exécution et le nombre d'erreurs commises.

Les différents tests utilisés par le laboratoire sont les suivants :

- test de poursuite visuelle compensée sur deux axes ou tracking,associé à une tâche secondaire de mesure du temps de réponse à l'extinction de feux colorés, il s'agit d'un test statique.

1. INTRODUCTION

Pendant de longues années les médecins de l'aéronautique ont vécu avec le dogme de l'incompatibilité de l'activité aérienne des pilotes avec la prise médicamenteuse. Aujourd'hui il apparait évident que le personnel navigant doit pouvoir bénéficier des préventions des complications de l'hypertension artérielle, des bénéfices apportés par les anti-histaminiques dans le traitement des états allergiques et peut être surtout dans la prévention des infestations parasitaires auxquelles peuvent succomber les personnels intervenant dans des territoires d'Outre-Mer.

La prise médicamenteuse ne peut non plus, être systématiquement refusée au personnel navigant en bonne santé mais soumis du fait de leur profession à des désordres fonctionnels. Les hypnotiques pris comme régulateurs du sommeil lors des ruptures du cycle nycthéméral veille-sommeil nous paraissent un exemple significatif. Enfin, en ce qui concerne l'état militaire, il est assez difficile d'envisager le concept d'opération continue sans l'aide de la pharmacopée pour répondre à la nécessité de diminuer l'état de fatigue des personnels, voire même à celle de supprimer totalement le sommeil sans altérer les capacités mentales et décisionnelles des personnels traitant l'information à un haut niveau de responsabilité. Mais en ce qui concerne l'aéronautique, le Général d'Armée Aérienne B. CAPILLON disait en inaugurant une conférence de l'OTAN-AGARD : "Evoluer dans l'espace n'est pas une activité naturelle de l'homme. Cette activité requiert à un degré particulièrement élevé une vigilance constante et des performances intellectuelles et physiques toujours intactes quelles que soient les conditions".

Pour protéger ce niveau élevé de vigilance et éviter toute diminution des performances intellectuelles, il va sans dire que les drogues utilisées par les médecins de l'aéronautique doivent être choisies sur des critères objectifs parmi les différentes possibilités offertes par la pharmacopée moderne.

Pour ce faire il est indispensable d'évaluer soit l'efficacité des médicaments psychostimulants, soit les effets secondaires indésirables sur la vigilance de toute molécule susceptible d'intervenir dans la thérapeutique ou la prophylaxie des maladies générales.

Cette évaluation de la performance, qui dépend du niveau d'attention, n'est pas chose aisée, surtout s'il s'agit de la mesurer dans un milieu aussi complexe que celui de l'aéronautique, où à la complexité de la tâche de travail, s'ajoute bien souvent une contrainte de l'environnement.

Il a donc été nécessaire d'analyser la tâche, ou ce que l'on appelle en ergonomie, le fonctionnement du couple homme-machine dans les diverses situations de travail, puis de mettre au point des tests simples mais dérivés des tâches réelles afin d'étudier avec précision tant l'action de ces contraintes sur la performance, que celle des médicaments à étudier.

Après avoir rappelé le fonctionnement de l'opérateur humain dans l'exécution d'une tâche complexe à la lumière des recherches effectuées dans ce domaine, les tests choisis et mis au point seront analysés et leur validation lors d'études de pharmacologie clinique, démontrée.

2. FONCTIONNEMENT DU COUPLE HOMME-MACHINE

Du point de vue ergonomique, la performance est définie comme la capacité à accomplir une tâche simple ou complexe en un temps limité, le plus court possible et avec le minimum d'erreurs ou d'omissions.

Elle est donc caractérisée par deux paramètres : le temps d'exécution et le nombre d'erreurs commises.

Mais de nombreux facteurs viennent bousculer cette apparente simplicité pour agir sur ces paramètres. Certains sont propres à l'individu, ce sont l'état physiologique et mental, l'état psychologique, le niveau de vigilance, le degré d'apprentissage. D'autres dépendent des contraintes de l'environnement dont les sources sont souvent multiples en aéronautique. Ces facteurs n'agissent pas sur la performance de façon indépendante. A ce titre il est évident que les contraintes extérieures retentissent sur l'état physiologique et psychologique du sujet mais peuvent en même temps compliquer la tâche. Le vol à basse altitude et grande vitesse est soudainement compliqué par la traversée d'une zone de turbulence dont les vibrations agissent aussi sur l'état physiologique du pilote.

D'autre part, l'influence des contraintes de l'environnement est fonction de la complexité de la tâche à accomplir. Plus celle-ci est délicate, plus la dégradation de la performance est sensible.

Les données concernant le fonctionnement du couple homme-machine ont suivi l'évolution de la cybernétique et de la théorie des asservissements, à un moindre degré des acquisitions de la psychologie moderne, en particulier des théories des conduites de Piaget.

Quoi qu'il en soit le couple homme-machine peut fonctionner soit en système ouvert, soit en système asservi selon la tâche à exécuter.

Dans le premier cas, la réponse de l'opérateur humain n'a bien entendu aucun retentissement sur la grandeur d'entrée du système. Le plus souvent la grandeur d'entrée est un signal visuel ou auditif. Ce schéma de fonctionnement, extrêmement fréquent dans l'industrie, existe en aéronautique dans la détection de cible ou dans la surveillance des écrans radars. L'exécution du travail nécessite un niveau d'attention élevé et continu alors que les signaux sont en général rares, aléatoires et fugitifs. Il s'agit de ce que l'on appelle une tâche de vigilance. Dans ce cas la performance est caractérisée par le temps de réponse de l'opérateur, c'est-à-dire le temps écoulé entre l'apparition du signal caractéristique et sa détection d'une part, le nombre d'erreurs ou d'omissions commises, d'autre part.

Il existe de nombreuses façons d'étudier la performance à ce type de tâche, tant en situation réelle que simulée et la mise au point de tests particuliers ne s'avère pas nécessaire.

Il n'en est pas de même lorsque le système homme-machine fonctionne en boucle fermée. En effet, dans ce cas, l'opérateur humain doit jouer à la fois et sans délai, le rôle de comparateur entre les entrées et la ou les grandeurs de consignes et le rôle de commande du système effecteur de correction. Les entrées étant le plus souvent des signaux visuels, il s'agit d'une tâche de poursuite. Cette poursuite peut être simple ou bien compensée. Dans le premier cas l'opérateur suit une cible sur l'écran à l'aide d'un index mobilisé par une commande manuelle. Il connait à la fois la grandeur d'entrée du système (le déplacement de la cible) et sa réponse.

Dans le second cas l'opérateur ne perçoit que l'écart entre l'entrée et sa précédente réponse qu'il doit s'efforcer d'annuler.

Ce type de tâche de contrôle est extrêmement répandu aussi bien dans les activités civiles que militaires. Ainsi, le pilotage d'un aéronef ou d'un véhicule automobile, le contrôle d'une machine outil à commande manuelle, sont autant de situations pratiques dans lesquelles les caractéristiques du contrôle visuel et manuel par l'opérateur sont d'une importance capitale pour la qualité de la performance du couple homme-machine.

Ces concepts ont donné lieu à d'importants travaux de modélisation de la performance entre les années 1950 et 1965. Ces recherches ont permis d'une part, des évaluations prédictives de la performance et de notables améliorations ergonomiques, notamment en matière de présentation des informations et de réalisation des organes de commande. D'autre part, ces modèles de représentation mettent en évidence les principaux paramètres à prendre en compte pour évaluer la performance et qui sont : l'écart de la réponse par rapport au signal d'entrée et son déphasage dû au retard introduit par l'opérateur.

La description détaillée des différents modèles établis dépasse très largement le cadre de cet exposé, mais disons qu'à la suite des travaux de RUSSEL (1951), HALL (1957), KRENDEL (1960), SHERIDAN (1962) et ADAMS (1961) on s'est orienté vers des modèles mathématiques quasi-linéaires dans lesquels la tâche de l'opérateur humain est représentée par la fonction de transfert entre la grandeur d'entrée ou erreur observée et la grandeur de sortie représentée par l'action sur la commande. Outre le gain, plusieurs paramètres sont pris en considération, tels que le temps de conduction neuro-musculaire, etc...

Ces modèles rendent bien compte du gain, du retard et du déphasage apportés par l'opérateur humain, mais comportent l'inconvénient majeur de ne permettre aucune étude des phases transitoires, ni de prendre en compte l'apprentissage de l'opérateur.

3. MESURE DE LA PERFORMANCE PSYCHOMOTRICE EN LABORATOIRE

De nombreux tests de vigilance ont été proposés, soit pour mesurer le niveau d'éveil d'un sujet, soit pour maintenir celui-ci à un niveau donné, en général maximal. Ces tests permettent en général une évaluation plus ou moins fine des temps de réponse à des stimuli visuels, auditifs ou mixtes.

Mais dans la vie courante et notamment en situation de pilotage, il est bien exceptionnel que l'opérateur humain n'ait qu'une tâche simple et unique à effectuer. Le plus souvent on a affaire à une intrication de nombreuses tâches individuellement variables dans leur difficulté mais aussi dans leur

présentation. Elles peuvent en effet soit se succéder avec une périodicité aléatoire, soit se présenter ensemble. L'exécution de deux ou plusieurs tâches est en général difficile mais elle est possible surtout lorsqu'elles alternent à basse fréquence.

Il parait logique de supposer que lorsqu'une des tâches est facile, elle permettra l'exécution d'une ou plusieurs autres simultanément. A l'inverse, si l'exécution d'une tâche requiert toute l'attention de l'opérateur il est vraisemblable que la superposition d'une nouvelle tâche, aussi facile qu'elle puisse être, saturera les possibilités de traitement de l'information.

Cette hypothèse n'est valable qu'à la condition que l'opérateur humain soit théoriquement capable d'exécuter deux tâches différentes se présentant simultanément à lui.

Il n'est pas certain que l'on puisse répondre par l'affirmative à cette question. La majorité des psycholoques du travail pensent que le cerveau humain ne peut traiter deux informations simultanées, l'une est mise en mémoire aussi longtemps que le traitement de l'autre information n'est pas terminé, puis elle sera traitée à son tour.

Quoi qu'il en soit on constate chez l'opérateur humain des changements de mode opératoire lorsque la charge de travail augmente, lui faisant adopter une tactique qui évite la surcharge difficile à supporter ou qui s'accompagnerait d'une dégradation du travail (SPERANDIO 1976).

L'opérateur humain n'apparait pas aussi figé que l'ordinateur auquel on s'est plu à le comparer même si au total ses capacités de traitement ou de mise en mémoire sont plus faibles.

Ainsi la charge de travail liée au pilotage possède divers degrés et autorise en général la détection de voyants de panne. Dès lors il existe une hiérarchisation des tâches. Le pilotage proprement dit est la tâche principale ou primordiale, la tâche secondaire consistant à détecter et à traiter des informations aléatoires situées parfois aux limites du champ sensoriel, c'est la détection des signaux d'alarme.

Pour ces raisons la simulation des tâches de pilotage a le plus souvent recours, soit à la superposition de plusieurs tâches de vigilance, soit à la combinaison d'une tâche principale et d'une tâche de vigilance considérée comme secondaire. POULTON (1960) a aussi montré la permanence de l'exécution normale de la tâche principale au détriment de la tâche secondaire de vigilance lorsque la quantité d'informations à traiter augmente. C'est à ce type de test que BRONN et POULTON (1961) ont fait appel pour étudier la conduite automobile.

C'est encore ce type de tâche qui a été utilisé pour l'étude des contraintes de l'environnement sur la performance psychomotrice que ce soit BURSILL dès 1958 pour l'étude de l'influence de la chaleur ou HOLLAND 1967 et SCHOENBERGER 1967 pour l'étude des effets des vibrations. Il s'agit presque toujours d'une tâche centrale de poursuite sur un ou plusieurs axes et d'une ou plusieurs tâches périphériques de vigilance utilisant le plus souvent des signaux lumineux, mais parfois aussi sonores ou mixtes.

3.1. - Test de poursuite visuelle ou tracking

Le dispositif que nous avons utilisé dérive de celui mis au point au laboratoire par AUFFRET et col. (1971). Il a l'avantage de présenter des caractéristiques asssez proches de tâches réelles tout en comportant des éléments opératoires facilement analysables. La tâche de poursuite compensée que nous traitons comme la tâche principale s'apparente à celle du pilotage en ce sens qu'elle constitue un système en boucle fermée à contre réaction négative représenté par un ajustement sensoriel et moteur continuel, la réponse du sujet modifiant en permanence la position dans l'espace du signal qu'il perçoit.

Enfin notre tâche a l'avantage de pouvoir être exécutée pendant une durée prolongée sans susciter ni fatigue excessive ni aversion du sujet. De plus son apprentissage est assez rapide et reste longtemps à un niveau stable.

Il est actuellement bien établi que le niveau de performance pour une tâche donnée est fonction d'une part du niveau de vigilance allant du sommeil aux états émotionnels ou d'hyperexcitation et du niveau d'activité des centres nerveux, c'est-à-dire de la fréquence et de l'intensité des stimuli, d'autre part.

Ceci nous a amené à associer à notre tâche principale, une tâche secondaire de vigilance permettant du fait de la fréquence des stimuli, un niveau d'activité des centres nerveux correspondant à une veille attentive.

La tâche principale choisie pour étudier la performance psychointellectuelle est une poursuite visuelle compensée sur deux axes, appelée tracking. Les informations constituant cette tâche sont présentées sur un cadran dérivé d'un système d'aide à l'atterrissage par mauvaise visibilité (ILS).

Ce cadran à deux aiguilles croisées est placé sur un bâti métallique face à l'opérateur humain et à 0,7 m environ de ses yeux.

Les aiguilles correspondent chacune à un axe horizontal ou vertical. Elles se déplacent selon un programme enregistré sur magnétophone. Il s'agit de deux sinusoïdes dont la tension crête est constante, mais la fréquence variable entre 0,1 et 0,05 Hz de façon aléatoire. Les deux sinusoïdes sont déphasées entre elles.

Au cours du test l'opérateur doit maintenir les deux aiguilles orthogonales au centre de l'instrument par l'intermédiaire d'un manche de commande miniature placé devant lui sur une table.

Les écarts de position des deux aiguilles par rapport à l'axe horizontal ou à l'axe vertical constituent les erreurs commises par l'opérateur sur chacun des deux axes concernés. Ces écarts sont traités dans un calculateur analogique qui fournit par sommation, un score d'erreurs exprimé en unités machines pour la période du test, obtenu après comparaison de la réponse du sujet et du score idéal gardé en

mémoire.Ce calcul est effectué séparément pour les deux axes, gisement ou localizer et site ou glide.

La tâche secondaire de vigilance est une tâche de détection et d'extinction de signaux lumineux. Il s'agit de deux lampes situées sur un axe horizontal au niveau des yeux de l'opérateur et sur le même plan que le cadran de présentation de la tâche principale de poursuite. Les lampes sont à 0,45 m de part et d'autre du cadran. La lampe gauche est rouge, la lampe droite est verte, l'une et l'autre s'allument de façon indépendante et aléatoire.

Dès qu'un signal est perçu, le sujet doit appuyer sur un bouton de commande d'extinction placé sur une poignée gardée dans la main non occupée par le micromanipulateur du tracking.

Ce test contemporain de la tâche principale et de même durée permet la présentation de 16 signaux lumineux.

L'intervalle de temps entre deux allumages successifs varie de façon aléatoire. Il est compris entre 25 et 60 s.

Il est possible de mesurer le temps qui s'écoule entre l'allumage d'une lampe et son extinction par le sujet avec une précision de l'ordre de $\pm$ 5 mS.

Ce temps, visualisé sur un voltmètre digital est imprimé automatiquement sur papier sous forme numérique. Il permet le calcul pour chaque test d'un temps moyen d'extinction des feux colorés rendant possible l'appréciation du temps de réponse global de l'opérateur à un stimulus d'alarme visuelle et de juger de son état de vigilance.

3.2. - Test de mémorisation immédiate

La performance psychomotrice a été appréciée par un test de mémorisation permettant d'apprécier l'empan moyen de la mémoire immédiate tout particulièrement sollicitée dans les tâches du type pilotage aéronautique.

Ce test baptisé VIGIL MEMO est une adaptation d'un test mis au point par la division de psychologie expérimentale du Centre de Recherche du Service de Santé des Armées.

Il est programmé sur un mini ordinateur. Un nombre de trois à dix chiffres est présenté au sujet pendant un temps proportionnel au nombre de chiffres composant le nombre.

Dès la fin de l'affichage, à un signal sonore, l'opérateur doit, à l'aide du clavier du calculateur reproduire le plus rapidement possible le nombre qui avait été affiché.

Si la réponse est correcte un nouveau nombre quelconque,mais ne commençant jamais par zéro, incrémenté d'un chiffre est alors présenté au sujet dans les mêmes conditions.

Au contraire, si la réponse est erronée, un nombre quelconque mais décrémenté d'un chiffre est présenté.

Le test complet comprend six séries de dix séquences de nombres affichés. Toutefois seules les cinq dernières séries sont prises en compte, la première permettant seulement au sujet d'arriver à ses capacités maximales de mémorisation puisque la première séquence de la deuxième série commence par l'affichage d'un nombre en rapport avec le nombre de chiffres de la dernière séquence de la première série. Il en est de même pour chacune des autres séries. Les résultats sont donnés pour chacune des séries par le nombre moyen de chiffres retenus et le temps moyen nécessaire à leur reproduction avec leur écart type.

En effet le temps d'affichage du nombre est fonction du nombre de chiffre qui le constituent. Par ailleurs, le logiciel est capable de prendre en compte le temps de réponse du sujet, y compris le temps d'exécution qui dépend de sa dextérité manuelle.

3.3. - Test de poursuite visuelle de cible sur coupole

Il s'agit d'un test dynamique mis au point récemment au laboratoire.

Le dispositif consiste en un système tournant constitué d'un ensemble mécanique mu par un moteur couple et d'un boitier électronique d'asservissement en vitesse. Ce système peut être commandé par un générateur de fonction ou recevoir des commandes en provenance d'un calculateur. Ainsi des profils de vitesse et d'accélération très divers peuvent être délivrés par l'ensemble tournant. Sur ce plateau tournant a été monté un siège avec un support de levier de commande d'un réticule en site et en gisement, un bras support de miroir, un bras de fixation au sol et une potence support du dispositif optique fixée sur le plateau tournant mais qui peut être dissociée du siège.

Le dispositif optique comporte deux ensembles distincts. Tout d'abord un écran de projection hémisphérique réalisé en matière plastique transparente. Cet écran est placé de telle sorte que son axe coïncide avec l'axe de rotation du système tournant.

Ensuite le projecteur de cible et de réticule est constitué d'un sytème opto mécanique placé au dessus du sujet qui projette sur la face interne de la demi sphère le faisceau d'un laser Hélium-Néon. Ce faisceau est divisé en deux branches secondaires : la première simule la cible, elle est pilotée en site par le calculateur et demeure fixe en gisement.La deuxième simule le réticule, elle est pilotée en site et en gisement par le sujet.

Le système opto mécanique est commandé par une électronique mise au point au Centre d'Essais en Vol.

Enfin un système informatique comprenant un calculateur DIGITAL PDP 11-23 et un système d'exploitation permet la commande du système tournant et du système optique et l'exploitation des résultats en temps réel.

4. APPLICATION A LA PHARMACOLOGIE

L'étude de la vigilance d'un opérateur humain qui permet la mise en oeuvre des tests décrits ci-desus trouve plusieurs applications en pharmacologie :

- Etude des effets secondaires de bon nombre de molécules employées dans la pharmacopée. Cet aspect de la pharmacologie clinique revêt une importance toute particulière lorsqu'il s'agit de travaux visant à la maîtrise pharmacologique des états de veille et de sommeil afin d'optimiser les performances opérationnelles et plus encore lorsque l'opérateur visé conduit une machine aussi sophistiquée qu'un aéronef de combat.

- En corollaire à cette première application on trouve l'étude des effets secondaires de certains produits pharmacologiques chez des sujets placés en situation de contrainte aéronautique (altitude, accélérations, vibrations...) ces effets secondaires pouvant alors être amplifiés par l'environnement particulier lié aux conditions de vol.

- Enfin, il est possible au contraire d'étudier des molécules susceptibles d'améliorer les performances généralement dégradées par ces mêmes contraintes aéronautiques. Dans ce cas, le sujet est alors probablement placé en situation apportant une dégradation de sa performance.

Dans ces différentes optiques le Laboratoire de Médecine Aérospatiale a testé les effets sur le niveau de vigilance d'un certain nombre de molécules dont nous donnerons ici quelques exemples.

Ces études ont été menées selon le même schéma habituel à la pharmacologie clinique. Elles ont porté sur douze sujets adultes de sexe mâle, âgés de 22 à 49 ans et dont le poids est compris entre 65 et 78 kg.

Les sujets volontaires mènent une existence active. Ils sont en bonne condition physique et psychique et sont entraînés depuis longtemps aux tâches psychomotrices que nous avons décrites au précédent chapitre.

L'étude est conduite en double insu contre placebo et parfois par comparaison des effets de la molécule étudiée avec une molécule de même famille pharmacologique prise comme référence.

Le traitement statistique des résultats obtenus fait appel à la théorie d'analyse de variance décrite par SCHEFFE en 1959.

Sous la double hypothèse de la normalité des distributions et de l'indépendance entre moyennes et variances, les calculs de l'analyse de variance ont été effectués selon un plan en facteurs croisés (LELLOUCH et LAZAR 1974).

Trois facteurs qualitatifs sont utilisés : l'un d'eux correspond à l'organisation du protocole en blocs complets, un bloc étant identifié à un sujet. Il s'agit donc de l'effet "sujet". Sa prise en compte permet l'estimation de la variabilité interindividuelle de façon à l'éliminer de l'erreur aléatoire.

Le second est le facteur "médicament" il décrit l'influence de la molécule active ou du placebo sur les résultats observés.

Enfin le troisième facteur permet d'appréhender l'évolution de la mesure des paramètres psychophysiologiques retenus en fonction de certaines grandeurs caractéristiques de l'expérimentation. En ce qui concerne nos études, il s'agit, soit du temps permettant de prendre en compte l'évolution du score entre le premier et le second test, autrement dit l'effet fatigue, soit de l'altitude.

L'analyse permet, outre l'estimation de la signification des trois facteurs décrits, celle de l'estimation de la signification du terme d'interaction entre les deux facteurs expérimentaux "médicament" et "fatigue". Ce test permet d'évaluer l'influence réciproque de ces deux facteurs l'un sur l'autre. Autrement dit, il permet de répondre à la question de savoir si la fatigue apparue au cours de l'essai est constante en fonction du "médicament" reçu.

Les autres tests statistiques restent inclus dans l'erreur aléatoire. Les résultats de ces différentes estimations sont donnés par le test "F" de Fischer-Snedecor.

Après l'estimation de signification de chacun des facteurs expérimentaux retenus, une analyse plus fine des résultats est effectuée sous la forme d'une comparaison des différentes moyennes deux à deux. Le test choisi est le test "t" de Student ou le test "g" dit du "range studentisé" selon les conditions d'application respectives de ces deux tests.

Quoi qu'il en soit le dénominateur de chacun de ces deux tests utilise l'erreur aléatoire telle qu'elle est calculée par l'analyse de variance.

4.1. - Etude en altitude du RU 24722

Cette molécule des Laboratoires ROUSSEL-UCLAF est un vasodilatateur central sans effets périphériques.

De ce fait il est intéressant d'évaluer les effets de ce produit sur des tâches d'attention et de vigilance d'un opérateur humain placé en conditions d'hypoxie hypocapnique d'altitude. L'altitude de 5500 m correspondant à une baisse de cinquante pour cent de la pression barométrique standard au sol avait été retenue. Cette altitude a été maintenue pendant toute l'expérimentation dans le caisson à dépression du Laboratoire.

Chaque sujet, pris comme son propre témoin, a reçu successivement et dans un ordre aléatoire : le placebo et le RU 24722 sous trois posologies différentes établies comme suit :

Pendant trois jours, chaque sujet a pris trois comprimés par jour, puis un comprimé une heure avant le test, le quatrième jour. Les comprimés étaient dosés à 10, 20 et 30 mg de produit actif ou de placebo.

Un intervalle de temps libre de huit jours pleins a été aménagé entre chacune des quatre séquences.

Les tests ont toujours été pratiqués le matin et si possible à la même heure pour chacun des douze sujets.

Le protocole expérimental était le suivant :
Une fois le sujet installé, un test au sol est effectué. Il comprend un tracking avec extinction de feux colorés et le test de mémorisation.

A l'issue, l'altitude de 5500 m (50,5 kPa) est réalisée. La vitesse de dépressurisation du caisson a été maintenue constante, égale à 17 kPa/mn. Dès l'arrivée à 5500 m, un test de tracking est effectué suivi d'un test de mémorisation de chiffres.

A l'issue, un second tracking est effectué, lui même suivi du test de mémorisation. Puis la pression du sol est rétablie.

Les résultats n'ont pas montré de modification statistiquement significative des tests utilisés en hypoxie d'altitude sous l'effet d'une prise de RU 24722. Par contre, le test de poursuite est altéré par l'hypoxie d'altitude au risque de 1 p. mille, de même que le temps de réaction globale.

Le test de mémorisation est altéré en altitude au risque de 1 p.cent.

4.2. - Etude de la MEDIFOXAMINE 50

Cette molécule des Laboratoires ANPHAR-ROLLAND est un psychotrope du type anti-dépresseur et anxiolytique doué en outre de propriétés antisérotonine, antispasmodique et analgésique.

Du fait de l'importance de la consommation de ce type de médicament, souvent par automédication, il nous a paru intéressant d'évaluer les effets d'une administration de MEDIFOXAMINE à doses répétées pendans quatre jours sur la performance psychomotrice d'un opérateur humain.

Chaque sujet a reçu pendant trois jours 2 comprimés de MEDIFOXAMINE 50 mg ou de placebo avant les repas du matin, de midi et du soir. Le quatrième jour 2 comprimés étaient absorbés avant le repas du matin. Les tests psychomoteurs étaient subis entre 1 h et 3 h après cette prise unique. Chaque sujet a alternativement effectué deux séries de chaque test : avant l'administration de toute molécule, puis 1 heure et trois heures après la dernière administration de MEDIFOXAMINE 50 ou de placebo.

Une pose thérapeutique de 10 jours a été pratiquée entre les deux séquences de prise du médicament ou du placebo.

Les résultats ont montré une amélioration du test de poursuite compensée par la MEDIFOXAMINE. Cette amélioration est significative au risque de 1 p. cent. Par contre le médicament s'est avéré sans action sur le temps de réaction global ni sur l'empan moyen de la mémoire immédiate étudiés par nos tests.

L'effet fatigue est lui aussi statistiquement significatif, montrant un allongement du temps de réaction entre les deux tests au risque de 1 pour mille.

Par contre l'interaction "médicament-fatigue" n'est pas significative,ce qui exclut une partitipation de la MEDIFOXAMINE dans la fatigabilité observée au cours du test.

4.3. - Etude de l'ASTEMIZOLE

L'ASTEMIZOLE est un antihistaminique des Laboratoires JANSSEN-LFBRUN.

Compte tenu du rôle de ce type de médicament dans les traitements des états allergiques et tout particulièrement respiratoires si fréquents chez le personnel navigant, il nous a paru utile d'étudier le retentissement de la molécule sur des tâches permettant d'apprécier l'état de vigilance d'un opérateur humain.

Cet éventuel effet secondaire de la molécule a été recherché en comparaison avec celui d'un antihistaminique de référence : la CHLORPHENIRAMINE.

Trois séquences ont été randomisées, l'une correspondant à l'ASTEMIZOLE, la seconde à l'antihistaminique de référence et la troisième enfin à un placebo.

Chaque sujet a reçu alternativement la dose d'ASTEMIZOLE, de CHLORPHENIRAMINE ou de placebo prise le matin des tests sous forme de deux comprimés ingérés à jeun. Aucune prise alimentaire n'a eu lieu entre l'absorption médicamenteuse et les tests passés entre une et deux heures après la prise du produit. Chaque séquence a été séparée par trois semaines de wash out.

Chaque test était constitué de deux tâches de poursuite suivies de deux épreuves de mémorisation.

Les résultats de l'étude statistique des différents éléments de la tâche de poursuite montrent que la performance n'est pas modifiée par l'ingestion d'ASTEMIZOLE alors que le niveau de vigilance est significativement diminué par la CHLORPHENIRAMINE.

Par ailleurs aucun des deux antihistaminiques n'interfère avec la mémoire immédiate, ni dans un sens, ni dans l'autre.

4.4. - Etude du DEBRUMYL

Le DEBRUMYL, commercialisé en France par les Laboratoires INAVA est un pychostimulant physiologique, capable de favoriser la coordination psychomotrice et d'améliorer la qualité du travail humain en permettant la rapidité de son exécution et en diminuant le risque d'erreur.

Nous avons étudié l'action de ce produit chez des sujets soumis à des vibrations mécaniques solidiennes sinusoïdales de 18 Hz à 1,6 G RMS d'amplitude pendant une heure.

Les sujets ont absorbé pendant quinze jours deux ampoules à midi, et une le soir de DEBRUMYL ou de placebo. Afin de disposer de points de référence du point de vue vibratoire, un jour sur deux les sujets effectuaient les tests psychomoteurs mais sans subir de phénomène vibratoire, c'est à dire sur un siège immobile.

Les résultats ont montré que des sujets exposés pendant une heure à des vibrations mécaniques de tolérance limite, selon la Norme ISO, dégradent légèrement mais significativement leur performance. L'absorption de DEBRUMYL, à la dose de trois ampoules par jour, entraîne une protection statistiquement significative avec une moindre dégradation de la performance,en particulier dans le dernier quart d'heure de l'exposition aux vibrations.

On constate, en outre, sous l'action du DEBRUMYL, une amélioration significative de l'ensemble des tests de performance des sujets placés dans les mêmes conditions expérimentales, mais ne subissant pas de vibrations.

5. CONCLUSIONS

Les contraintes de l'environnement peuvent rendre insupportable une charge de travail mental jusque là très bien tolérée et ce bien avant l'apparition des dérèglements des grandes fonctions physiologiques et a fortiori des lésions structurelles connues comme étant les effets physiopathologiques de ces contraintes. C'est particulièrement le cas en aéronautique où les contraintes du vol et de l'environnement ne sont chez le personnel navigant qu'en surimpression sur la contrainte que représente le travail du pilotage ou de navigation.

S'il est dans un certain nombre de cas parfaitement licite de simuler cette charge de travail, encore faut-il que cette simulation soit raisonnable.

En pharmacologie le problème n'est pas très différent. Lorsqu'on veut apprécier les effets directs ou secondaires d'une thérapeutique, on est amené à s'intéresser à l'impact du médicament sur la performance psychomotrice, autant qu'à ses effets cardiovasculaires, digestifs ou respiratoires.

C'est pour tenter d'évaluer le niveau de vigilance d'un opérateur humain soumis à des contraintes de l'environnement, soit aux effets pharmacologiques d'une drogue, soit à l'association des deux, que le Laboratoire de Médecine Aérospatiale du Centre d'Essais en Vol a mis au point des tests psychomoteurs s'adressant, soit à la mémoire immédiate, soit à des tests de poursuite en boucle fermée, soit encore à la mesure du temps global de réponse à un signal d'alarme lumineux.

L'association de ces tests proposés permet manifestement, grâce à un traitement approprié fondé sur l'analyse de variance, d'évaluer la variabilité interindividuelle toujours élevée lors de l'expérimentation en psychophysiologie humaine, mais surtout cette méthode, qui permet d'appréhender les effets secondaires d'une prise de médicament sur le niveau de vigilance est, en outre, assez sensible pour permettre la distinction des effets d'une contrainte de l'environnement, telle que l'altitude, de ceux d'une éventuelle thérapie intercurrente.

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Discussion

Nicholson, UK

We've been looking at the effects of various antihistamines, like yourself, on performance and indeed one of the interesting developments in pharmaceutics at the moment is that there are several antihistamines now available in which one cannot detect any effects on performance, at least in the dose ranges that one is interested in studying. As far as astemizole is concerned we have rejected that drug for use in the RAF and also in the civil airlines because it takes it about four or five days before it has any effect, any antiallergic effect, and then it has an elimination half life somewhere around about 12 days, and in fact a single oral dose of this drug will modify skin responses to histamines for periods up to about 30 days. We are rather concerned with astemizole because of its very prolonged action. The possibility of any idiosyncratic effects, if they appeared they would be persistent and als the possibility of drug interactions. I wonder, what is the position in your world as to how you are making decisions as to whether these drugs should be made available to aircrew. As far as the UK is concerned, we now recommend trephenadine which is the Merrill-Dow antihistamine and that is now used by civil aircrew and by RAF aircrew as well.

Poirier, FR

(reply not translated)

EFFET DE L'ACETYL-DL-LEUCINE SUR LA PERFORMANCE DU REFLEXE VESTIBULO-OCULAIRE CHEZ L'HOMME.

Par

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Les propriétés anti-vertigineuses de l'Acetyl-dl-Leucine ont été mises en évidence il y a plus de vingt cinq ans par LEAU et DUCROT (12). En se fondant sur le comportement postural post-rotatoire de lots de souris, ces auteurs ont examiné l'effet anti-vertigineux de nombreuses substances, en particulier des amino-acides. Parmi ceux-ci, le dérivé Acétylé de la Leucine s'est révélé particulièrement actif.

Les études cliniques menées par la suite (5-8) ont confirmé l'intérêt de cette molécule en matière de thérapeutique anti-vertigineuse. Dans les études les plus récentes ((15, 16), le produit est classiquement décrit, sous sa forme injectable, comme un traitement efficace de l'accès vertigineux.

En fait, comme pour la plupart des anti-vertigineux et des anti-naupathiques, le site d'action exact de l'Acetyl-dl-Leucine reste dans le domaine des hypothèses.

Certains éléments, en particulier les différences de concentration importantes en amino-acides existant entre endolymphe et périlymphe (17), peuvent faire évoquer une action périphérique. Par ailleurs, la molécule peut constituer le précurseur d'un neuro-médiateur agissant sur l'une ou l'autre des structures nerveuses impliquées dans les mécanismes d'orientation spatiale.

En dehors des études cliniques et de l'utilisation de réponses globales, comme le comportement post-rotatoire, peu de travaux ont été consacrés au retentissement physiologique du produit sur la fonction vestibulaire. Il est donc apparu intéressant d'apprécier, d'une manière quantitative, le mécanisme intime de l'Acetyl-dl-Leucine sur un des aspects spécifiques de cette fonction : le réflexe vestibulo-oculaire (V.O.).

On sait en effet (3) que le VOR constitue un des sous-systèmes participant à la stabilisation de l'image rétinienne lors des mouvements de la tête. De nombreuses études ont été consacrées à ce problème complexe et la plasticité de ce réflexe dans l'espèce humaine a largement été discutée. La perturbation du fonctionnement normal du VOR est habituellement bien supportée après la période de compensation. Ces perturbations peuvent cependant aboutir dans certains cas à l'apparition d'oscillopsies.

De nombreuses substances antivertigineuses agissent en déprimant le capteur vestibulaire perturbant de cette façon le fonctionnement normal du VOR.

Ces perturbations peuvent avoir un impact négatif sur la performance psychomotrice d'opérateurs humains mettant en oeuvre des systèmes d'armes complexes.

Pourtant dans de nombreuses situations opérationnelles ces opérateurs sont soumis à des stimulations vestibulaires intenses qui peuvent elles mêmes perturber gravement la performance. Il est donc important, dans le domaine de la prophylaxie médicamenteuse des troubles de l'orientation spatiale,d'évaluer le retentissement secondaire des molécules employées.

1. - METHODES

1.1. - Sujets

Douze sujets volontaires, onze hommes et une femme, exempts d'affections vestibulaires pathologiques, ont participé à l'expérimentation.

1.2. - Dispositif expérimental

Les stimulations vestibulaires ont été délivrées par un fauteil tournant CONTRAVES-GOERZ. Les qualités mécaniques de ce système permettent d'obtenir des stimulations très pures et très reproductibles. Le fauteuil est couplé à un calculateur qui assure la gestion de l'expérimentation, la saisie des données et leur traitement.

L'enregistrement du nystagmus horizontal était réalisé au moyen d'une technique d'électro-oculographie (E.O.G.) classique, le sujet se trouvant dans une enceinte totalement obscure. Une calibration du signal E.O.G. était effectuée avant chacun des enregistrements composant une épreuve.

Le niveau de vigilance du sujet influence les caractéristiques observées du réflexe vestibulo-oculaire (10). Afin de diminuer le rôle joué par ce facteur, un test de discrimination auditive contrôlant la vigilance était effectué par le sujet pendant toute la durée des épreuves.

Enfin, pour les épreuves post-rotatoires, un dispositif potentiométrique permettait au sujet d'indiquer l'intensité des perceptions à l'arrêt selon un protocole décrit par d'autres auteurs (7).

1.3. - Protocole expérimental

Un protocole expérimental rigoureux a été observé pour les épreuves per et post rotatoires. L'application de ce protocole, en double insu, a comporté :

- L'administration en injection intraveineuse lente d'un placebo ou du produit (1 ampoule de 5 ml de TANGANIL, SPECIA) 45 minutes avant les épreuves.

Pour l'étude du nystagmus per-rotatoire, une excitation sinusoïdale de vitesse crête égale à 50 degrés/seconde a été appliquée en explorant successivement les fréquences de 0.01, 0.02, 0.04, 0.08 et 0.16 Hz.

Trois épreuves ont été réalisées pour chaque sujet, un test de référence et deux tests comportant l'injection du produit ou du placebo.

Pour les épreuves post-rotatoires les stimulations consistaient en des échelons de vitesses de 90°/s et 150 °/s, obtenus par l'arrêt brutal du fauteuil. Les sens horaires et anti-horaires ont été explorés avec un ordre de présentation en carré latin. De plus, on a pris soin de réduire au mieux l'effet d'habituation communément observé avec ce type de stimulation (6). Deux épreuves ont été réalisées à quinze jours d'intervalle, pour chaque sujet, avec placebo ou produit.

1.4. - Traitement des données

Le signal E.O.G. convenablement amplifié et filtré, était pris en compte par le calculateur afin de déterminer les paramètres significatifs du nystagmus.

Il est maintenant classique d'exprimer les caractéristiques du réflexe vestibulo-oculaire per-rotatoire en termes de phase et de gain, pour les fréquences explorées. Le logiciel de traitement utilisé lors de notre expérimentation a été décrit par PARMENTIER et LYNCH (14). Le signal de position de l'oeil est dérivé de façon à déterminer les vitesses de phase lente du nystagmus (Fig.1). On établit alors la moyenne des données obtenues lors des huit cycles de stimulation, constituant un test pour une fréquence donnée (Fig. 2). Cette procédure permet d'annuler certains artéfacts d'enregistrement et ramène la réponse en vitesse de l'oeil à un cycle de stimulation. On détermine alors la phase et le gain de la courbe cumulée de vitesse de l'oeil par rapport à la stimulation.

Le réflexe vestibulo-oculaire obtenu en post-rotatoire a été caractérisé au moyen de trois paramètres : la constante de temps de décroissance des vitesses de phase lente, le gain et l'amplitude cumulée de déplacement de l'oeil. A partir du signal de position de l'oeil, on applique un programme de traitement dont le principe est sensiblement identique a celui décrit par BARNES (1). Après élimination des saccades (Fig.3), on calcule la vitesse moyenne de chaque phase lente et l'on procède également à la cumulation de l'amplitude des phases lentes pour les trente secondes d'enregistrement. La courbe de vitesse des phases lentes en fonction du temps est ainsi établie pour chaque échelon de vitesse. L'opérateur désigne alors le début de la décroissance et le calculateur interpole l'exponentielle de décroissance (fig.4). La constante de temps du réflexe et son gain initial sont alors calculés.

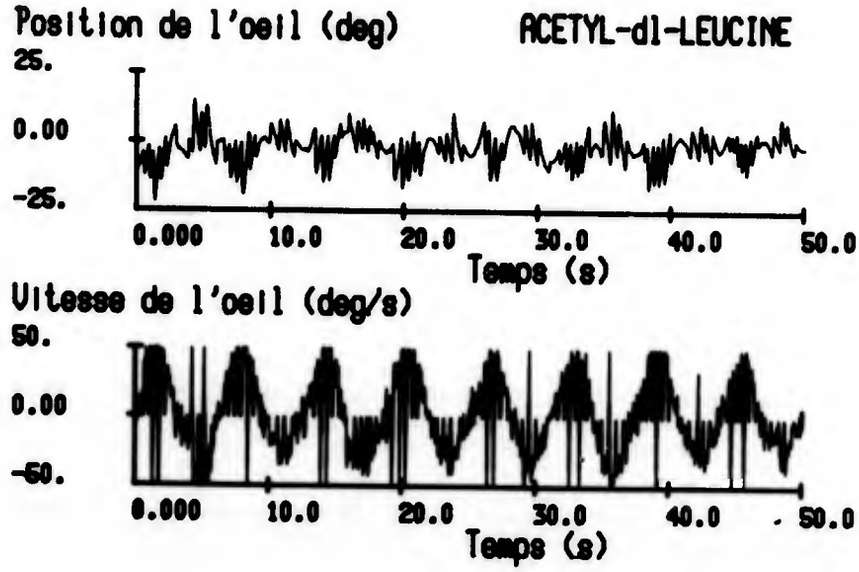

Figure 1 : Traitement du nystagmus per-rotatoire. Dérivation du signal de position de l'oeil.

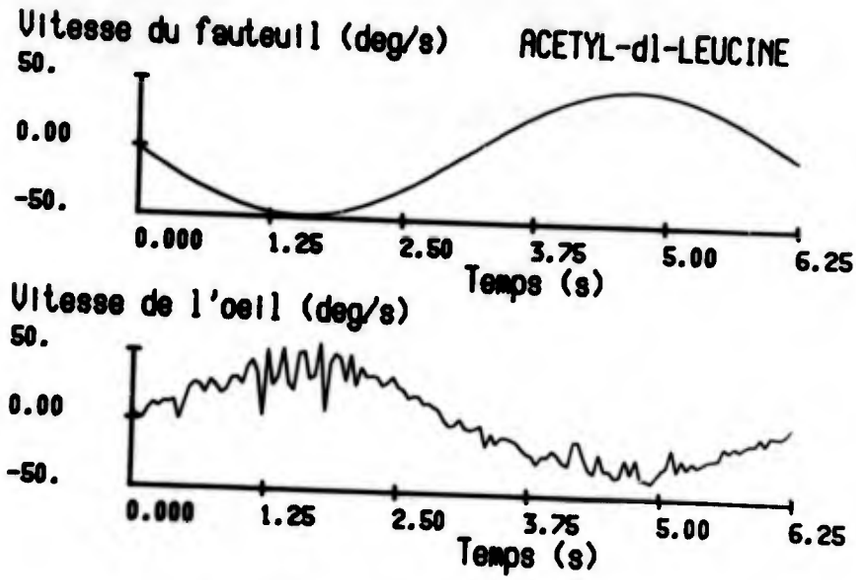

Figure 2 : Courbe cumulée de vitesses de phase lente de l'oeil pour le nystagmus per-rotatoire.

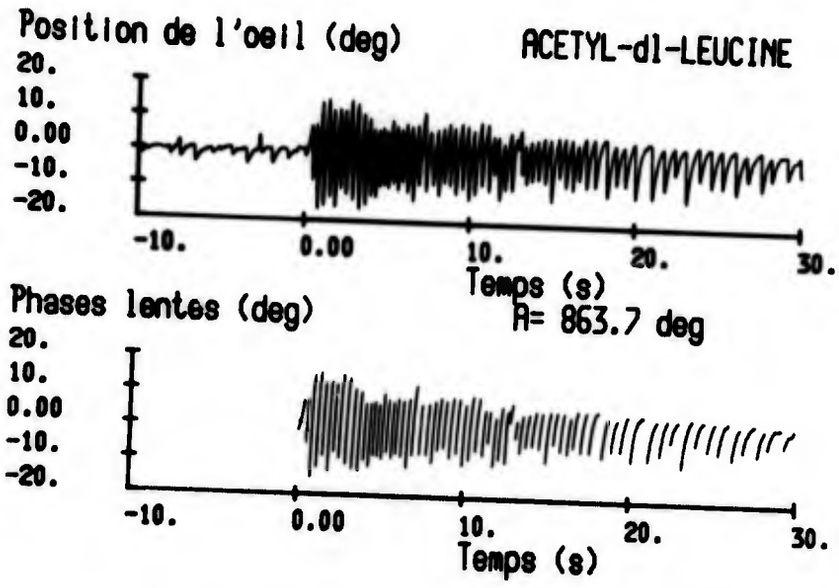

Figure 3 : Nystagmus post-rotatoire : Elimination des saccades et détermination de l'amplitude cumulée de déplacement de l'oeil.

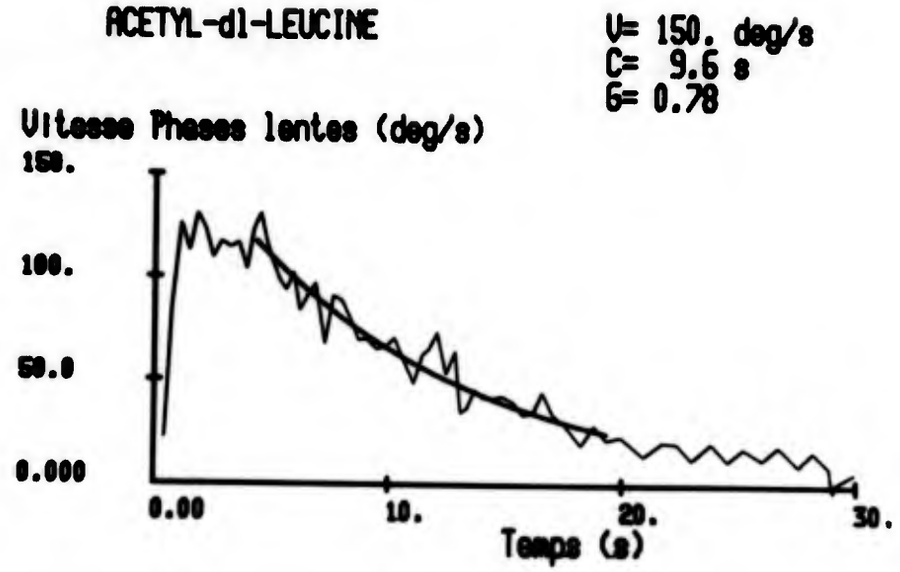

Figure 4 : Courbe de décroissance des vitesses de phase lente du nystagmus post-rotatoire.

2 . - RESULTATS

Les résultats obtenus en per et post-rotatoire sont présentés dans les figures 5 à 9. Nous envisagerons successivement les deux séries d'essais.

2.1. - Caractéristiques du nystagmus per-rotatoire.

Les caractéristiques de phase du réflexe vestibulo-oculaire en fonction des fréquences explorées sont présentées dans le diagramme de la figure 5, pour les essais avec l'Acetyl-dl-Leucine et le placebo. Les valeurs obtenues lors des épreuves de référence et celles provenant d'études sur une très grande population ne sont pas représentées sur cette figure. On constate qu'il n'existe pratiquement pas de différence entre les résultats obtenus avec le placebo et le produit. De même, il n'existe pas de différences significatives entre ces valeurs et celles obtenues lors des tests de référence sans produit.

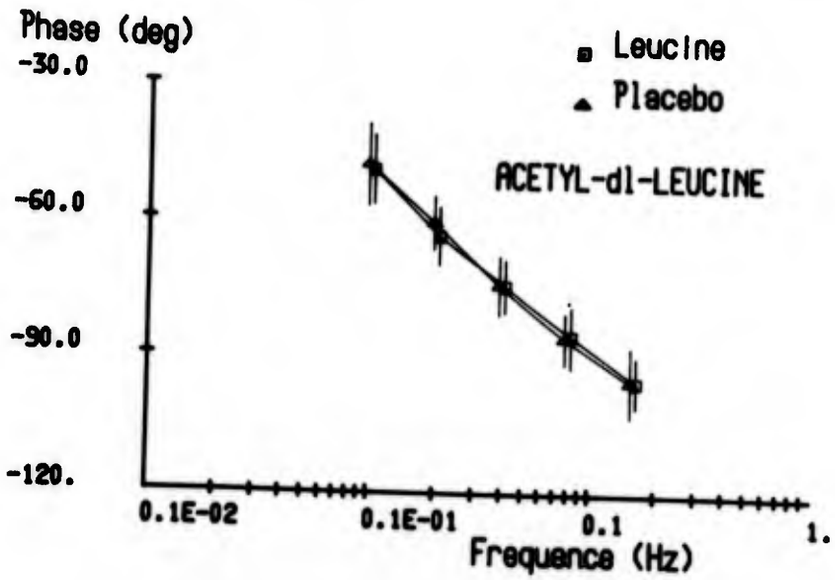

Figure 5 : Caractéristiques de phase du réflexe vestibulo-oculaire per-rotatoire avec Acetyl-dl-Leucine et placebo.

Le diagramme suivant (fig.6) donne les valeurs du gain du réflexe obtenues en fonction des fréquences de stimulation, pour les épreuves avec le placebo et la Leucine. En dépit des variations introduites au niveau des gains par les fluctuations du niveau de vigilance, les valeurs mesurées sont relativement homogènes. Là aussi, on constate que les valeurs obtenues sous Acetyl-dl-Leucine ne diffèrent pas de celles avec placebo.

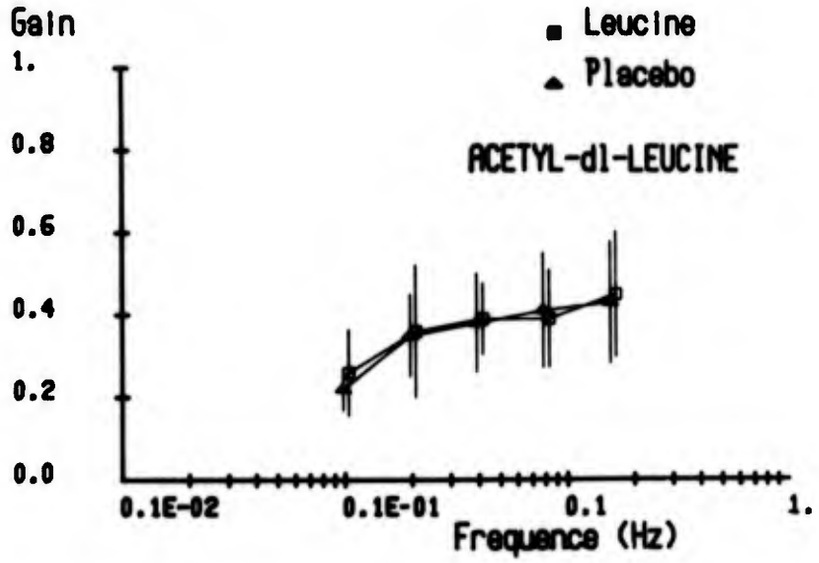

Figure 6 : Caractéristiques de gain de réflexe vestibulo-oculaire per-rotatoire avec Acetyl-dl-Leucine et placebo.

2.2. - Nystagmus post-rotatoire

L'examen des valeurs observées pour les différents paramètres représentatifs du nystagmus post-rotatoire permet de constater que l'habituation a été minime entre les deux séries de tests. La faible différence existant en moyenne entre la première et la deuxième série n'est en aucun cas significative sur le plan statistique.

Les valeurs moyennes de décroissance des vitesses de phase lente rencontrées pour les différents échelons de vitesse sont présentées à la figure 7. L'importance de l'écart-type signe la variabilité inter-individuelle élevée. Les valeurs relativement faibles de ces constantes de temps montrent que la population étudiée ne peut être considérée comme naïve. On ne relève aucune différence qui soit significative sur le plan statistique.

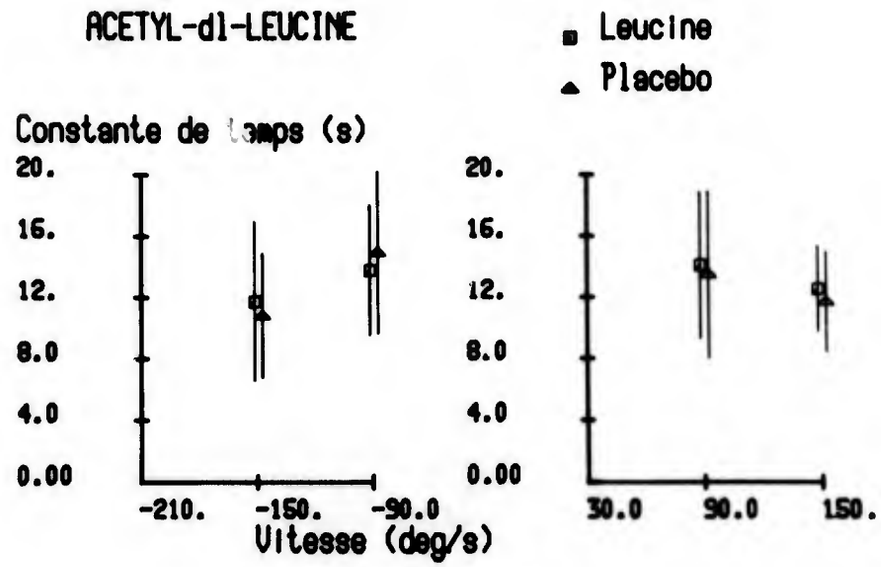

Figure 7 : Constante de temps de décroissance des vitesses de phase lente du nystagmus post-rotatoire.

Il en va de même pour les valeurs des gains au maximum de vitesse qui sont présentées à la figure 8. Toutes ces valeurs restent dans le domaine de ce qui est couramment décrit dans la littérature (7).

Enfin , les valeurs des amplitudes cumulées de déplacement de l'oeil observées pour les différents échelons de vitesse pendant les trente secondes d'enregistrement ne révèlent aucune différence entre les deux traitements (fig. 9).

L'estimation subjective de l'intensité de la sensation post-rotatoire s'est révélée très décevante. Il existe en effet des différences inter-individuelles très importantes rendant difficile l'exploitation de ces données. De plus, on constate parfois une discordance entre les estimations comparatives verbales et celles obtenues au moyen du dispositif potentiométrique.

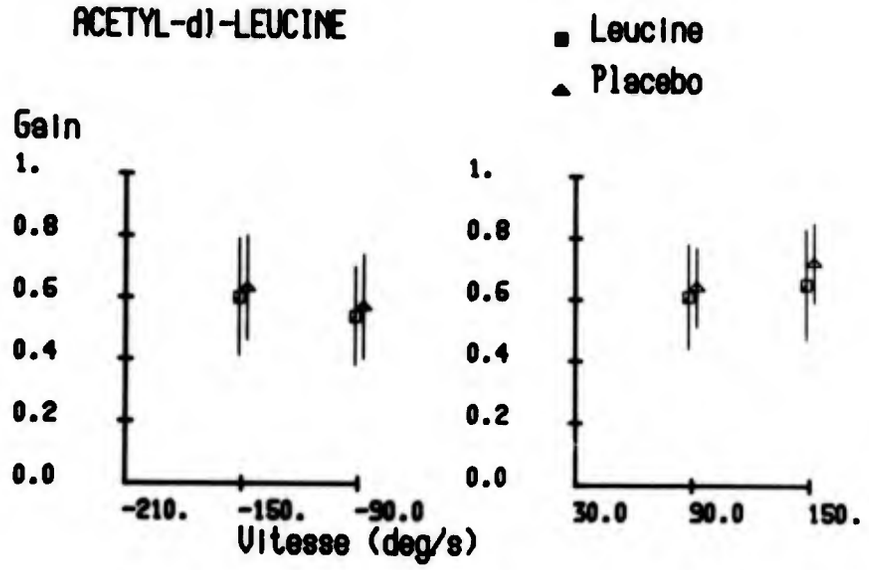

Figure 8 : Gain initial du réflexe vestibulo-oculaire post-rotatoire.

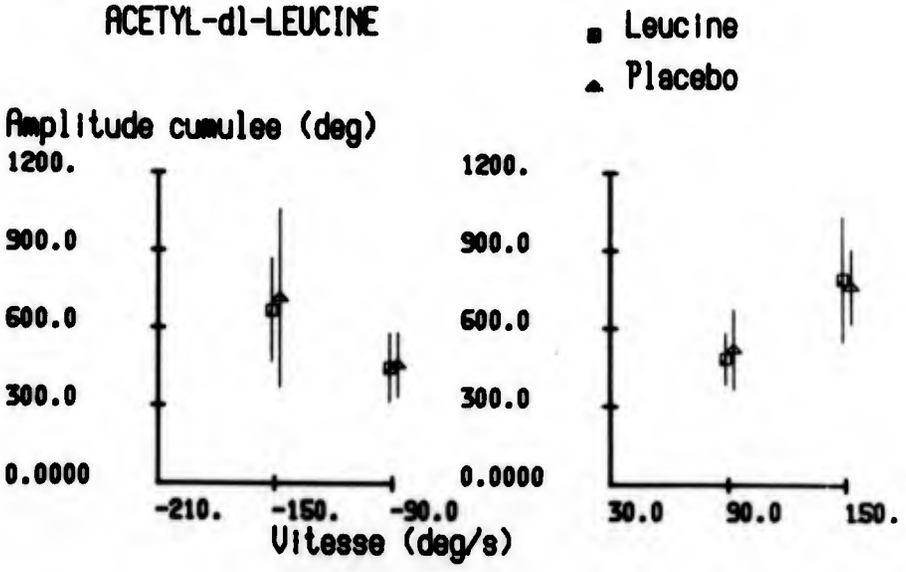

Figure 9 : Amplitude cumulée de déplacement de l'oeil en post-rotatoire.

3. - DISCUSSION

Les résultats démontrent clairement, que chez le sujet sain, l'Acetyl-dl-Leucine employée à dose thérapeutique par voie intraveineuse ne modifie pas les caractéristiques quantitatives du réflexe vestibulo-oculaire.

Ces observations ne permettent donc pas de confirmer les résultats obtenus par OOSTERVELD (13), chez l'animal et chez l'homme. Cet auteur, travaillant avec des stimulations sinusoïdales délivrées par un fauteuil pendulaire, a décrit une diminution significative de la durée du nystagmus avec l'Acetyl-dl-Leucine.

La notion de durée des périodes nystagmiques est étroitement liée aux autres paramètres quantitatifs, c'est-à-dire le gain et la phase de la réponse oculaire. Il parait donc difficile d'envisager une inhibition de la durée de la réponse sans modification de la vitesse de phase lente du nystagmus. Par contre, JAGER et HENN (9) ont montré l'existence de phénomènes d'habituation de la réponse oculaire aux stimulations sinusoïdales, ce qui pourrait peut être expliquer les différences observées.

D'un autre côté, BENSON ET BRAND (2) ont décrit des modifications du nystagmus post-rotatoire avec la scopolamine, sans que les vitesses de phase lente et la constante de temps soient modifiées. La scopolamine, qui est un anti-naupathique majeur, induit des modifications de forme et de durée de la réponse oculaire ainsi qu'une nette réduction de la sensation post-rotatoire.

Dans ce cas, il semblerait que des modifications portant sur la durée de la réponse aient été observées sans modification concomitante des paramètres quantitatifs pris en référence dans notre étude. Ceci suggère que, compte-tenu de la complexité du système vestibulaire, les paramètres élémentaires décrivant la réponse compensatoire de l'oeil, phase et gain, ne rendent pas entièrement compte des interactions à l'intérieur du système.

De toute façon, l'absence de réponse physiologique chez le sujet sain, ne peut exclure totalement la possibilité d'une action régulatrice du produit sur un système vestibulaire pathologique. Ce mode d'action a, en effet, été suggéré par certains auteurs en particulier par GABERSEK et Coll. (10) pour d'autres molécules.

Il est également possible d'envisager une action beaucoup plus centrale de la Leucine, qui, agissant au niveau des aires corticales associatives, atténuerait la perception vertigineuse sans modifier le message sensoriel périphérique. On pourrait alors concevoir un effet anti-vertigineux sans action sur les réflexes vestibulaires. Notons à ce sujet que des études récentes menées par BUTTNER (4) ont montré, sur la base d'expériences psycho-physiques et d'enregistrements unitaires, que les aires vestibulaires corticales pourraient jouer un rôle plus important que celui qui leur est classiquement attribué.

Sur le plan des effets secondaires généraux de la molécule on peut considérer qu'elle est très bien tolérée. Il n'existe pas de retentissement notable sur le niveau de vigilance ainsi qu'on a pu le contrôler lors des épreuves vestibulaires.

4. - CONCLUSIONS

L'Acetyl-dl-Leucine, dont l'action anti-vertigineuse semble cliniquement bien établie, s'est révélée à dose thérapeutique et chez le sujet sain, dénuée d'action sur certaines caractéristiques du réflexe vestibulo-oculaire. Il semble que l'on puisse, dès lors, exclure une action directe de la molécule au niveau du capteur vestibulaire et des structures nerveuses impliquées dans le réflexe.

L'action antivertigineuse de ce produit reste donc relativement inexpliquée mais semble préserver le fonctionnement des asservissements physiologiques contrôlés par le système vestibulaire. Ce fait pourrait être considéré comme potentiellement intéressant en matière de prophylaxie des troubles de l'orientation spatiale. Il ne faut toutefois pas négliger la possibilité de ne voir le produit agir que dans des conditions pathologiques.

Deux hypothèses peuvent être avancées pour tenter d'expliquer ces résultats :

Ou bien, les paramètres étudiés ne reflètent pas la totalité des interactions complexes survenant au sein du système vestibulaire, ou bien l'action éventuelle de la Leucine doit être envisagée à un niveau plus élevé dans l'élaboration de la perception vertigineuse. La molécule agirait alors en supprimant cette sensation bien plus au niveau central qu'à celui de la perception périphérique.

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HOMEOSTATIC, ENTRAINMENT AND PACEMAKER EFFECTS OF DRUGS THAT REGULATE THE TIMING OF SLEEP AND WAKEFULNESS

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SUMMARY

The timing of wakefulness and sleep in humans, and other diurnal primates such as the squirrel monkey (*Saimiri sciureus*), is influenced not only by the duration of prior wakefulness or prior sleep, but also by the phase of the circadian timing system. In continuous, round-the-clock operations, or with transportation between time zones, conflicts frequently occur between these determinants of arousal state. The predictive circadian component favors wakefulness and sleep at phases consistent with the recent history of environmental and internal time cues. On the other hand, the reactive homeostatic component is principally determined by the length of prior wakefulness on the particular day in question.

Investigations of pharmacological agents which influence the timing of sleep and wakefulness indicate they may exert their effects directly on the neuronal/humoral mechanisms responsible for the generation of sleep (homeostatic effect), or by altering the phase of the circadian system. The circadian effects may either be achieved by resetting the phase of the circadian pacemaker (pacemaker effects) or may act by influencing the interaction between environmental light-dark cycles and circadian pacemakers (entrainment effect). Examples of drugs which appear to have predominantly homeostatic effects (e.g. muramyl dipeptide), pacemaker effects (e.g. sodium valproate) or entrainment effects (e.g. diazepam) will be discussed. An appropriate strategy for the management of alert wakefulness at any hour of day and night must use the appropriate pharmacological tools to manage circadian and homeostatic components of wakefulness and sleep.

LIST OF SYMBOLS

τ = Circadian Period

ϕ = Phase of Circadian Rhythm

$+\Delta\phi$ = Phase Advance

$-\Delta\phi$ = Phase Delay

In recent years pharmacological strategies have been extended into another dimension--that of time. Not only do many drugs have different efficacies and effects depending on the time of day when they are administered (1), but also certain pharmacological agents can reset the timing of circadian pacemakers (2). Once fully characterized, the clock-resetting properties of such drugs can be exploited to adapt humans to changing time schedules. If ignored, these agents could even act against their intended purpose. A sleeping pill that induces sleep might also reset in the wrong direction the neurophysiological pacemakers that govern the natural timing of the circadian sleep-wake cycle.

In view of these potentially conflicting effects, it is essential to differentiate between the direct effects of a drug on a physiological function from the effects induced by altering the timing of the biological pacemaker which generates rhythms in that physiological function. It is the purpose of this talk to present a system for classifying drugs in terms of "homeostatic" (H), "entrainment" (E) and "pacemaker" (P) effects and to discuss examples of drugs which illustrate each of these properties.

Nowhere are these distinctions more important than in the regulation of sleep and wakefulness. As we move into a twenty-four-hour-a-day global community, in which continuous operations, rotating shifts, night work, and travel across time zones become common, our innate timekeeping mechanisms come into conflict with our artificial schedules. It has become essential to develop a set of pharmacological tools for manipulating the natural timing of the sleep-wake cycle as the situation demands.

To appreciate the basis for our proposed classification scheme, it is first necessary to review briefly the factors that determine the timing, duration and quality of sleep. It is increasingly apparent that these characteristics of sleep and sleep stages are influenced not only by the duration of prior wakefulness but also by the phase of the circadian timing system. The relative importance of these factors is important to quantify since conflicts may at times occur between the predictive circadian component, which favors sleep at a phase consistent with the recent history of environ-

mental and internal time cues, and the reactive homeostatic response to prior wakefulness (3).

Homeostatic Regulation of Sleep

It has long been recognized that sleep serves a recovery function, allowing the conservation, storage and restoration of depleted energy and other physiological requirements (4,5,6). The conceptualization of sleep as a homeostatic regulatory response to deficits accumulated during wakefulness derives largely from the fact that sleep deprivation results in an increased probability sleep onset and the lost sleep is, at least in part, compensated for in subsequent sleep episodes. In the extreme case, sleep appears to be essential for life since prolonged sleep deprivation results in severe pathology and death (7). Recently evidence has been presented that certain peptides accumulate during wakefulness and are metabolized during sleep, and may act as sleep-promoting factors (e.g. factor S) (8,9).

The compensatory increase in sleep duration that follows sleep loss is rarely complete--a result which was originally considered inconsistent with the idea that sleep was homeostatically regulated. A solution to this problem, however, came with the realization that sleep involves an intensity dimension in addition to duration. Studies in several species show an increase in the proportion of recovery sleep spent in deep sleep (characterized by high amplitude slow waves in the cortical EEG and corresponding to stages 3 and 4 in humans) and, in some cases, in REM sleep, at the expense of light (or stage 2) sleep (10,11,12,13,14,15,16,17,18,19,20). Slow-wave sleep also increases in training athletes after strenuous exercise, although apparently not in other subjects (21,22). Slow-wave sleep decreases following extended sleep (23) or afternoon naps (24). Delta waves, in fact, appear to be homeostatically conserved in that nocturnal delta-wave parameters are reduced in proportion to the amount of delta activity exhibited during a daytime nap (25). Quantification of the EEG pattern obtained in NREM sleep has revealed increases in the density, duration and/or amplitude of delta waves (0-0.5 hz to 3-4 hz) or in EEG power density in that frequency range following sleep deprivation (26,13,27), as well as a decrease in these parameters following extended sleep (28).

Circadian Regulation of Sleep

Most organisms, including humans, have endogenous neural pacemakers which generate circadian (approximately 24-hour) rhythms in a wide range of physiological functions including sleep. In mammals the suprachiasmatic nuclei (SCN) of the hypothalamus act as the circadian pacemaker. Through a phase modulation by neural inputs responding to the illumination of the retina, the SCN maintain the sleep-wake on a daily schedule appropriate to the environmental timing of night and day. These pacemaker rhythms are self-generated; when an individual is isolated from environmental time cues, the sleep-wake cycle will "free run" at its natural period, which often differs from the twenty-four hour day. Humans, for example, have an endogenous circadian period of typically twenty-five hours. The sleep-wake cycle may be entrained to other periods close to its natural period, usually by the appropriate light-dark schedule. Hence we are normally entrained to a twenty-four hour period by the twenty-four hour alternation of night and day. However, the pacemaking system has significant inertia. An abrupt change in the environmental schedule may require several cycles before reentrainment occurs, leading to the difficulties that people experience in changing work shifts or time zones.

The mechanism of entrainment to light-dark cycles has been extensively characterized in mammals (although not yet directly in humans). Brief light pulses phase-shift the free-running activity rhythm of animals living in constant darkness by differing amounts and direction depending on when (i.e., at what phase) the stimulus was given. By measuring such phase shifts in response to light pulses given at different phases of the circadian cycle, a phase response curve (PRC) can be constructed. Such PRCs have been recognized as a universal feature of the mechanism of entrainment to all effective stimuli in a wide variety of species, from unicellular algae to primates (29,30,31). Furthermore, PRCs for light pulses in all species, whether nocturnal or diurnal, share the following general properties:

1. Phase delay shifts ($-\Delta\phi$) occur when the stimulus is early in the subjective night of the animal.

2. Stimuli late in the subjective night cause phase advance shifts ($+\Delta\phi$).

3. The response system is relatively insensitive (no phase shifts) during most of the subjective day.

These curves describe the capacity of the system to phase advance or phase delay under free-running conditions. Entrainment of circadian rhythms to a 24-hour day is

accomplished by periodic stimuli which cause a phase shift each day equal in amount to the difference between the natural period of the pacemaker (τ) and 24 hours. Entrainment to other day lengths is necessarily limited to a range of values around τ, called the range of entrainment (ROE), which is related to the maximum resetting capacity of the system in each direction as described by the PRC. Since the amplitude and exact shape of the PRC vary between species and among individuals (32), the ROE does as well.

In man, the synchronized circadian system can be entrained to period lengths ranging from about 23.5 to 26.5 hours. This means that there is only a very limited capability for resetting circadian rhythms in any one 24-hour period. This explains the lack of tolerance that humans show to schedules which require acute shifts in the timing of sleep and duty hours.

The neural pathways involved in this entrainment by environmental light-dark cues utilize a specialized group of retinal ganglion cells and a monosynaptic "retinohypothalamic tract" (RHT) from the retina to the suprachiasmatic nuclei. The SCN respond to the level of incident illumination on the retinae rather than the patterns utilized in visual perception. Light at dawn and dusk, in particular, by falling on the photosensitive portion of the PRC achieves the daily modulation of the phase of the circadian suprachiasmatic pacemaker, and therefore the sleep-wake cycle.

Mechanisms of Actions of Drugs That Influence the Timing of Sleep

From the above discussion, it can be seen that the timing of sleep could be manipulated using pharmacological agents which affect any one (or more) of the various mechanisms that influence the timing, duration or quality of sleep. In broad terms, a drug may influence either the neuronal centers responsible for the generation of sleep and its homeostatic function or the circadian pacemaking system which influences the timing of the endogenous sleep-wake cycle. Furthermore, drugs which manipulate the phase of the circadian system may either directly reset the phase of the circadian pacemaker, or may alternatively influence the interaction between the light-dark cycle and the pacemaker.

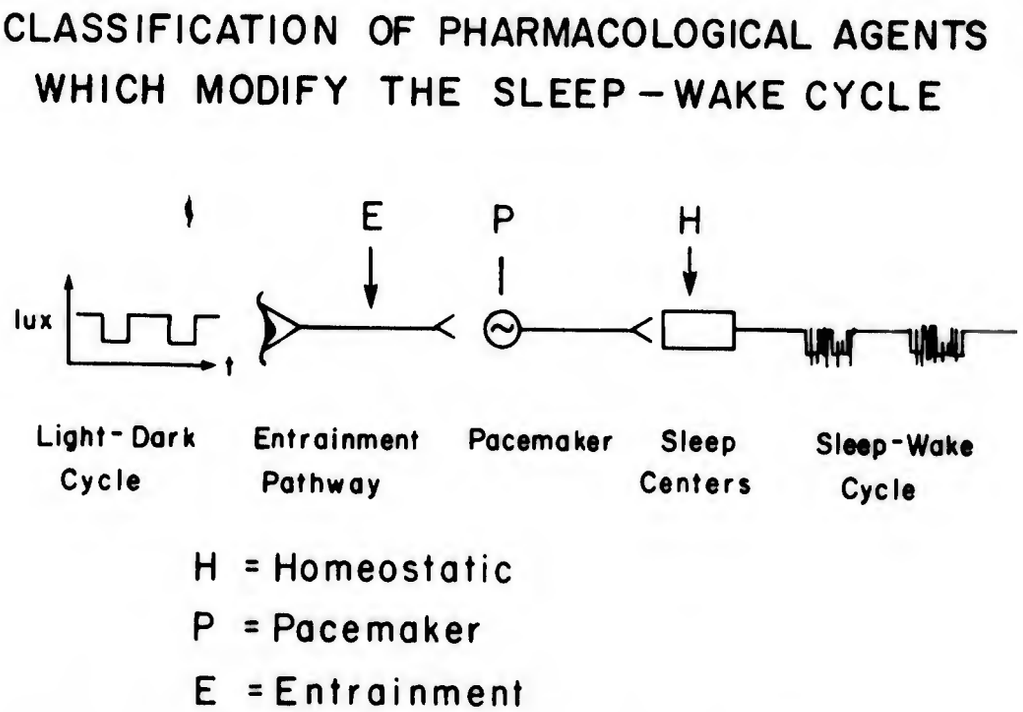

FIG. 1

Figure 1 summarizes the types of pharmacological actions that could result in an alteration in the timing of sleep and wakefulness. Drugs which induce pure "H" effects on the homeostatic sleep processes may induce sleep at an altered time of day, but on cessation of treatment, the sleep-wake cycle will instantaneously resume at its original circadian phase. Drugs with "P" effects directly on the phase of the circadian pacemaker, however, will cause a phase-resetting of the sleep-wake cycle which will persist after treatment (depending on the resultant phase achieved). Finally, drugs with "E" effects on the entrainment mechanisms will have phase-resetting effects on the circadian pacemaker that will depend on the light or dark stimulus being applied at that time.

It should be emphasized that these are operational rather than anatomical definitions. It will be important for therapeutic purposes to determine whether agents are dependent on the incident light intensity for their effect. However, a drug with an "E" effect may be acting on the retina, RHT, or even in the SCN on neurons which are responsive to RHT inputs. One way of distinguishing these criteria more rigorously will be to compare PRCs derived in LL, DD and optically-enucleated animals. In the latter the RHT degenerates and if the PRCs in LL and optically-enucleated animals are similar, it is safe to conclude that the drug has a "P" effect rather than an "E" effect. No two PRCs will be absolutely identical; for one thing, the environmental light intensity influences the circadian period of the pacemaker. However, phase-advance and phase-delay sections of a PRC which are of comparable timing and magnitude can be accepted.

Drugs With Predominantly "H" Effects

An example of a drug that effects sleep without affecting its circadian timing is muramyl dipeptide (MDP), a factor S analog as well as an immunoadjuvant and pyrogen (33). In squirrel monkeys individually housed in temporal isolation in constant light, we have studied the effect of 50 nmol of synthetic MDP injected either one hour after wake-up time (subjective day) or just before sleep time (subjective night). At both phases, decreases in percent time awake (relative to saline controls) were observed. After administration of MDP early in the subjective day, the animals exhibited alert wakefulness only 47.4% of the subjective day, compared with a mean 86.7% of subjective day after a saline control injection. MDP given at the circadian late subjective day resulted in sleep and transitional episodes occupying 84% of the subjective night vs. 73% of time asleep after control injection. Despite the marked influences of MDP on the sleep-wake pattern over the 24-hour period after administration, the circadian timing system demonstrated no consistent shifts in phase. MDP in squirrel monkeys thus appears to modify sleep-wake states by mechanisms that do not require phase resetting the circadian timing system, and hence by our classification would act with an "H" effect.

Drugs with Circadian ("P" or "E") Effects

Pharmacological agents which shift the phase of the circadian pacemaker thereby manipulate the neurophysiologic mechanisms that generate circadian rhythms, and not just the expression of the sleep-wake cycle on the day of treatment. A pacemaker-resetting drug is characterized by its lasting effects on the circadian rhythms of the individual; after discontinuation of the drug, the rhythms (depending on the phase of treatment) would typically not revert to their previous phase, but would be subsequently reset to a new initial phase.

A variety of pharmacological agents have been shown to influence the period or the phase of the circadian system. They include such chemicals as deuterium oxide (heavy water) and lithium, which lengthen the natural period of the circadian pacemaker in a variety of species from plants to mammals (34,35). Agents where full PRCs have been documented include the methyl xanthines, theophylline (36) and caffeine (37); certain protein synthesis inhibitors, such as chloramphenicol (38); and puromycin (39,40,41,42), the ionophore valinomycin (43,44), and ethanol (45,44). It is interesting that some of these agents are present in the beverages we commonly drink while flying. However, we normally take these with no regard to the time of day and do not consider their potential effect on our biological clocks.

Agents which alter the activity of the neurotransmitter GABA are of particular interest. GABA receptors are found throughout the brain, but in their highest concentrations in the hypothalamus. It is of particular interest that the SCN contain the highest concentration of the glutamate dehydrogenase enzyme, which synthesizes GABA from glutamate (46).

One GABA agonist with an effect on the primate circadian system is sodium valproate which enhances GABA synthesis and inhibits its degradation. Oral doses of valproate comparable per unit body weight to those prescribed for human psychiatric therapy were given to squirrel monkeys, free-running in individual cages under constant light. Within days, valproate consistently caused either a lengthening or a shortening of period in individual animals; the squirrel monkeys could be divided consistently into two groups of equal size, those that lengthened and those that shortened their period. Valproate is used in the treatment of acute mania, particularly in lithium-non-responders, and inter-individual differences in circadian response may well account for the differing therapeutic efficacy in different individual patients (46).

Distinguishing Between "P" and "E" Effects

We have discussed the significance of distinguishing between pacemaker (P) and entrainment (E) effects. Drugs with each type of effect will ultimately reset the phase of the SCN and will therefore influence the phase of the circadian sleep-wake cycle.

However, agents with "E" effects can block or inhibit stimuli derived from light input, thus appearing like a dark pulse administered in constant light. However, in constant darkness or an optically-enucleated animal, where there is no light input to be modulated, the phase response characteristics would be significantly different. In contrast, a "P" compound will display a similar PRC irrespective of the animal's lighting conditions. A clear operational distinction between "P" and "E" effects can thus be made if the full PRCs for both constant light and constant darkness are known.

Some headway has been made in distinguishing between entrainment and pacemaker effects in the investigations that we and others have conducted with benzodiazepines. The benzodiazepines, including diazepam (valium), flurazepam (dalmane) and triazolam (halcion), are GABA agonists and potent, widely-prescribed hypnotics. Recently diazepam and triazolam also have been discovered to have circadian resetting properties, but where are they acting? GABA receptors are not only found in the SCN, but also in the retina and the lateral geniculate nuclei, both components of the pathways through which light information is conveyed to the SCN. Thus the benzodiazepines could have either "P" or "E" effects (or both).

Many of the studies of benzodiazepine circadian phase-resetting actions have been conducted in hamsters. The "H" effects of benzodiazepines seem to be minimal in this species even at relatively large doses. Within minutes of treatment they are running on their wheels again. The first reports by Ralph and Menaker showed that large intraperitoneal injections of diazepam in hamsters free-running in constant darkness could block light-pulse-induced phase advances, but not light-induced phase delays (47). However, at the two times of the cycle they studied, insignificant phase shifts were caused by diazepam alone. This suggests that diazepam has an entrainment effect, but only during late subjective night when light pulses cause phase advances. Ralph and Menaker speculated that diazepam acted on retinal GABA receptors, but that light input followed two separate neural pathways to the SCN for delays and advances, and only the advances passed through GABA-inhibited neurons.

Figuring that if diazepam blocked light pulses it would simulate the application of dark pulses if animals were treated in constant light, we gave the same dosage of diazepam I.P. as Ralph and Menaker to free-running hamsters in constant light, and derived a PRC very comparable to a dark pulse PRC at all phases of the day. Although this could imply that diazepam has an "E" effect rather than the "P" effect, the other explanation (i.e., that the PRC represents a direct action of diazepam on the pacemaker irrespective of the light-dark schedule) could not be ruled out without determining the PRC to diazepam in constant darkness.

Such a test of benzodiazepine action has been provided by Turek and Losee-Olsen who determined the PRC for a large dosage of triazolam (halcion, a more potent but shorter-lived hypnotic benzodiazepine) in two groups of hamsters, one free-running in constant light, and the other in constant darkness (48). While those in constant light displayed a PRC comparable to that of diazepam and dark pulses, those in constant darkness also displayed a similar PRC. Obviously a PRC in darkness could not be produced by simulated dark pulses, so the benzodiazepines appear to act directly on the pacemaker. Ralph and Menaker's blockage of light pulses can thus be interpreted as the light-induced phase advances being nullified by diazepam-induced phase delays, resulting in no net effect. However, close inspection of the two PRCs indicates there are still small differences between the constant light and constant dark PRCs; potentially benzodiazepines therefore act, in light, both on light input and the SCN. Further studies, in which diazepam or triazolam is applied intracranially or to optically-enucleated hamsters, may help settle this question.

Of course, benzodiazepines also have homeostatic effects on sleep; this is the basis for the millions of prescriptions that are written every year. By determining the "P" and "E" effects of benzodiazepines, we can increase treatment efficiency by formulating the best parameters for therapy. The pacemaker effects can be applied to complement rather than antagonize the hypnotic effects; knowing the entrainment effects, if any, we can compensate for environmental lighting conditions. Although some agents may have all three effects, it is useful to distinguish between them to ensure that the appropriate therapeutic strategy is used. Such a scheme, we believe, will facilitate further research into the mechanisms and therapeutic regimens for controlling sleep and wakefulness at times required by operational considerations.

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ACKNOWLEDGEMENT

Supported by AFOSR Grant No. 83-0194.

Discussion

Spencer, GE
You said that the pathway between the retina and the suprachiasmatic nucleus was monosynaptic and then proceeded to try and see if it is possible to find out if drugs are having a direct effect there. Wouldn't the problem be somewhat simpler if you know what the neurotransmitter of this pathway is, and if you do, what is it?

Moore-Ed, US
. . (not recorded). . the neurotransmitters in that pathway, there is some evidence for several transmitters being involved. The issue, however that we have been trying to tackle, has been if we can study in hamsters, optically enucleated animals, we can remove that by degeneration, that entire pathway can degenerate. Really we're looking for an operational definition, namely, does the impact of light per se influence the effect the drug has as a pacemaker resetter. And so that our direction right now is to look for that interaction and offer a new set of definitions, an operational set of definitions, rather than a neuron chemical set of definitions. That's our first approach to this. Subsequently, we are going to want to understand the neurochemistry, but I think before we understand the rather complex neurochemistry there are an awful lot of transmitters lurking in the SCN that we need to understand operationally as to which drugs influence or are interactive with the resetting properties of light-dark cycles.

Jones, US
Do you intend to see if the effect of light on the body, other than through the eye, might also have through the skin a direct photon stiumlation of the brain?

Moore-Ede, US
. . (not recorded). . one or two other species have extraretinal photoreceptors. To all intents and purposes it is not possible to demonstrate, in mammals, their existence. That optically enucleated animals, for mammals are for all intents and purposes insensitive to light. That's really not proved to be data that had been replicated outside some lizards and some birds. But in mammals it does not appear to be a problem.

Van Den Biggelaar, NE
Dr. Moore, on one of your graphs you showed us the minimum reaction times or maximum sleepiness times of aircrew. These were, as I recall, between 3 or 4 o'clock in the afternoon. . .

Moore-Ede, US
No, in the morning.

Van Den Biggelaar, NE
Oh, in the morning. OK, I'm sorry. That answers my question.

Moore-Ede, US
It is those early hours before dawn. As anybody in operational situations can well-attest, it is the hours before dawn.

Terrian, US
I believe you've shown quite clearly that determining the phase-response curves for pharmacological agents in this free-running condition can be a productive and meaningful approach to this research, but I hope I misunderstood you, you don't believe that it is premature to begin to try to dissect out the neurochemistry of the suprachiasmatic nucleus. And that it is a potentially fruitful and complimentary approach to this subject for your own research.

Moore-Ede, US
Oh, absolutely. The answer to the question previously was to say, that the definition, because of the problems of defining the differences between these drugs, because of the purposes of definitions at this time we use an operational definition. Does

light and the drug interact? Now that actually is of practical value in the first steps for us toward practical use of those agents. However, there is an enormously important area of research which is the neurochemistry of the SCN, the understanding of the interaction of those transmitters. That will be our route in the future towards the identification of drugs. And we may have to wait for drugs that have the effects we desire at doses which are tolerable to the individual. There is a very big dose problem which is unresolved as yet in this area.

Terrian, US

Well, as a neurochemist I appreciate that answer and I wonder if I could follow. I think there really are two transmitters that may code for light in central nervous system that are most promising. Certainly, acetylcholine, historically, and now with the data Menaker will present at the forthcoming neurosciences meeting where they have stimulated the optic fibers and have shown that non- and NMDA antogonists block the ability to stimulate the SCN, glutamate becomes a viable candidate. Don't you think that working with phase shift curves as they have been done classically in the past where they are light-induced and then look for pharmacological means of manipulating that, that would be a promising way of dissecting out the chemistry of the SCN?

Moore-Ede, US

It is certainly a promising way to dissect out the chemistry, but the challenge we've directly taken on is trying to look operationally at drugs that are being used and try to understand which of those you might have to be concerned about the interaction between sunlight and the drug at certain phases. Now, I think this is really a question in the aims of the institute we are forming associated with Harvard is to address both basic and applied questions in parallel because in fact the fruitful interaction will come in attacking both approaches. There are some things we have to do right now because people quite frankly are starting to prescribe drugs like halcyon and some of these other agents quite freely and we need to understand some of those interactions as soon as we can because there may be some undesirable effects that are lurking in there that not only interfere with the pilot's individual performance but may also cloud the interpretation of the data. But at the same time, I would be, I'm rarely accused of not putting a pitch in for basic research at the same time.

EFFETS RESIDUELS DES BENZODIAZEPINES HYPNOTIQUES SUR LA VIGILANCE ET L'EFFICIENCE DES PERSONNELS AU REVEIL

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RESUME

Pour détecter et évaluer les effets résiduels des benzodiazépines hypnotiques sur la vigilance et l'efficience des personnels au réveil, on a procédé à une étude en double aveugle de trois benzodiazépines hypnotiques utilisables pour des besoins militaires opérationnels.

Le plan expérimental a porté sur 16 sujets militaires (8 jeunes et 8 plus âgés) qui ont absorbé en prise vespérale et dans un ordre aléatoire à quatre jours d'intervalle les produits suivants : PLACEBO, LOPRAZOLAM I mg, TRIAZOLAM 0,25 mg, TRIAZOLAM 0,50 mg et FLUNITRAZEPAM I mg.

La vigilance et l'efficience au réveil ont été évaluées par une batterie de huit tests psychométriques (quatre tests papier-crayon et quatre tests informatisés sur micro-ordinateur) mesurant l'état subjectif au réveil, l'attention, l'efficience psychomotrice, la mémoire immédiate, la mémoire différée, le raisonnement numérique, l'efficience dans une tâche complexe et l'efficience en surcharge d'information. Chaque test comprenait huit formes parallèles (autant que de passations par sujet, compte tenu des passations "à blanc" en début et fin d'expérimentation). L'avantage des quatre tests informatisés était de mesurer non seulement la performance finale, mais aussi le déroulement de la passation (variation du temps de réaction à chaque réponse, coefficient de régularité et indice de fatigue entre le début et la fin du test).

Le programme d'exploitation statistique des résultats permettait de contrôler les éventuels effets de lassitude ou d'apprentissage dus à la répétition des tests et d'évaluer les différences inter-produits, inter-tests, inter-groupes et inter-individus.

Les résultats ont révélé l'existence d'une détérioration psychométrique infra-clinique, manifestée plus dans le déroulement de la passation que dans le score final des tests, et portant plus sur les fonctions intellectuelles supérieures (raisonnement, tâche complexe et surcharge d'information) que sur les aptitudes brutes (attention et mémoire). Toutefois, on a relevé des différences notables de détérioration entre groupes (jeunes et vieux), entre individus (sujets sensibles et sujets résistants) et entre produits (le FLUNITRAZEPAM I mg et le TRIAZOLAM 0,50 mg provoquent une détérioration résiduelle plus forte).

En conclusion, cette expérimentation révèle que les benzodiazépines hypnotiques ne sont pas dénuées d'effets résiduels. En contradiction avec l'état subjectif satisfaisant et l'efficience apparente conservée, les tests psychométriques révèlent une détérioration mentale infra-clinique au réveil, qui porte surtout sur les fonctions supérieures et les tâches complexes. Mais il est possible de limiter cet inconvénient en sélectionnant les produits les moins nocifs et les sujets les plus résistants.

TEXTE

I - La détection psychométrique des effets cliniques et infra-cliniques des drogues.

Les benzodiazépines offrent plusieurs intérêts militaires : pour prévenir ou réduire le stress, comme traitement (anticonvulsivant) préventif ou curatif des agressions de guerre chimique par produits organo-phosphorés et, en ce qui concerne les benzodiazépines hypnotiques, comme moyen pour maîtriser le sommeil, c'est-à-dire pour obtenir au moment voulu des sommeils réparateurs sans effets résiduels invalidants au réveil.

Ce dernier objectif a été particulièrement étudié ces dernières années par les chercheurs militaires, en particulier par NICHOLSON et par PARROTT au Royaume-Uni.

Toutefois, des observations cliniques attentives font état d'une baisse résiduelle de vigilance et d'une altération transitoire des capacités mentales (attention, mémoire, efficience psycho-motrice et raisonnement) chez des sujets au réveil après prise vespérale de somnifères du groupe des benzodiazépines. Ces altérations, "infra-cliniques", passent souvent inaperçues. D'une part, parce que le repos apporté par la nuit de sommeil produit un sentiment d'euphorie qui se traduit par une impression subjective d'aisance et de facilité dans l'exécution des tâches, quel que soit leur niveau réel de performance ; d'autre part, au plan objectif, parce que tout sujet en état de détérioration mentale discrète et transitoire parvient toujours à réaliser correctement une tâche moyenne ou un test bref en mobilisant sa "capacité de réserve" (KARLSBECK), quitte à retomber ensuite dans un état méconnu de détérioration infra-clinique.

D'où l'intérêt, pour détecter les détériorations infra-cliniques et évaluer les petites variations de performance, primo d'utiliser des tests très sensibles, secundo de procéder à des passations assez longues pour épuiser la capacité de réserve, tertio d'utiliser des tâches complexes qui mettent d'emblée en œuvre le maximum des capacités du sujet et pour lesquelles la capacité de réserve ne parviendra pas à combler le déficit d'efficience et, quarto, d'évaluer non seulement le score final du test mais aussi la manière de le passer et la stratégie de passation. En effet devant deux scores finals égaux, par exemple, on pourra discerner si tel sujet possède toutes ses capacités intactes et tel autre n'est parvenu à maintenir son niveau de performance en fin de test qu'en sacrifiant son temps de réponse ou en changeant de stratégie.

Pour ces objectifs, les tests psychométriques informatisés (sur micro-ordinateur, en particulier) offrent des avantages notables :

- stricte standardisation des consignes (sans influence du psychologue),
- réalisation de procédures interactives très proches des situations réelles,
- possibilité de faire varier rapidement la difficulté de la tâche requise jusqu'au point de rupture des capacités du sujet,
- rapidité et fiabilité des calculs des résultats,
- et, surtout, exploration et appréciation du déroulement de la passation (suivi des temps de réponse, détection des changements de stratégie, etc...)

II - Protocole expérimental.

On a procédé à une comparaison en double aveugle, et selon la méthode de l'essai croisé, de trois hypnotiques du groupe des benzodiazépines (flunitrazepam, loprozolam et triazolam) et d'un placebo chez 16 sujets militaires volontaires, tous de sexe masculin, répartis en deux groupes d'âge : un groupe de 8 sujets jeunes (20 à 25 ans) et un groupe de sujets mûrs (35 à 40 ans) ; cette division étant introduite pour contrôler le paramètre "détérioration physiologique" qui est censé s'exercer progressivement à partir de l'âge de 25 ans.

Les doses respectives choisies pour les trois hypnotiques ont été les doses habituelles prescrites en prise vespérale dans la pratique médicale courante, soit 1 mg pour le flunitrazépam, 1 mg pour le loprazolam et 0,25 ou 0,50 mg pour le trizolam (pour ce dernier produit, on a testé les deux dosages).

La présentation identique, sous forme de gélules, du placebo et des produits, rendait toute identification impossible tant pour le clinicien administrant le produit que pour le sujet se prêtant aux essais. En pratique, les gélules étaient présentées dans des boîtes individuelles numérotées de 1 à 16 (soit une boîte par sujet) comportant chacune 5 flacons étiquetés A, B, C, D et E et contenant chacun une gélule à prendre en respectant l'ordre de A à E le soir à quatre jours d'intervalle. En fait, l'attribution des gélules pour les flacons A à E, a été déterminée de façon aléatoire pour chaque sujet et n'a été dévoilée qu'après l'expérimentation.

Chaque sujet, comparé à lui-même au plan des performances psychométriques au réveil, et comparé aux autres sujets lors de l'exploitation statistique finale, a passé la batterie de tests huit fois, à huit heures du matin, avec quatre jours d'intervalle entre les passations. Les passations 1 et 2 ont eu lieu "à blanc" (sans prise de gélule) pour établir le niveau de performance au départ et contrôler l'effet d'apprentissage. Les passations 3, 4, 5, 6 et 7 ont correspondu aux prises des gélules A, B, C, D et E prises la veille au soir à 22 heures. La passation 8 a déterminé le niveau de performance en fin d'expérimentation, à blanc, quatre jours après la prise de la dernière gélule, soit à J. 28.

Tous les volontaires choisis étaient sains, c'est-à-dire ne présentant pas de détérioration mentale notable, ne souffrant pas de troubles du sommeil ou de la vigilance et ne prenant pas habituellement de somnifères.

III - Batterie de tests psychométriques.

Les tests psychométriques ont été choisis en fonction des objectifs mentionnés plus haut, c'est-à-dire la détection de la détérioration mentale infra-clinique, l'évaluation fine des petites variations de performance et la mise hors circuit de la capacité de réserve. On a fait en sorte, aussi, que la batterie de tests explore les principales capacités mentales impliquées dans les tâches d'efficience militaire : attention, mémoire visuelle et auditive, mémoire immédiate et mémoire différée, raisonnement, tâche complèxe et surcharge mentale. On y a joint un questionnaire d'auto-évaluation de la forme au réveil (pour contrôler l'état subjectif). En fin de compte, la batterie était composée de huit tests : quatre tests papier-crayon (trois tests d'efficience mentale et un questionnaire subjectif) et quatre tests d'efficience mentale ou psychomotrice, informatisés sur micro-ordinateur. La durée totale de passation était de 30 minutes, c'est-à-dire ni trop brève (afin de venir à bout de la capacité de réserve) ni trop longue (pour ne pas introduire un effet parasite de lassitude).

Les caractéristiques des huit tests de la batterie sont les suivantes :

1 - Test du double barrage (test papier-crayon).

C'est un test d'attention sélective à tâche complexe, appréciant la vigilance et l'attention . La tâche consiste à barrer le plus rapidement possible tous les signes correspondant à deux modèles (une lettre et un chiffre) sur 34 (25 lettres et 9 chiffres) dans une page de 1.000 caractères (25 lignes de 40 caractères) présentés apparemment dans un ordre aléatoire (en fait, il y a 20 signes à barrer dans la page). La correction tient compte du score (x/20) et du temps. Il existe huit formes parallèles du test.

2 - Test des damiers (test papier-crayon).

C'est un test de mémoire visuelle immédiate qui consiste à se remémorer l'emplacement d'un certain nombre de cases (de 1 à 5) sur un damier de 25 cases cases blanches immédiatement après la présentation brève (5 secondes) du modèle. Les modèles présentés successivement, au nombre de dix, sont de difficulté croissante. La tâche consiste à marquer d'une croix noire les cases retenues sur une feuille-réponse comportant 10 damiers blancs.

La cotation, simple, compte un point par modèle correctement reproduit, (soit y/10). Le test comprend huit séries parallèles, soit deux séries originales pouvant être présentées de quatre façons différentes, par rotation des côtés.

3 - Test des noms génériques. (Test papier-crayon)

C'est un test de mémoire auditive différée portant sur la rétention mnésique, au terme d'un délai de 30 minutes, d'une série de cinq mots associés à un nom générique et ordonnés par fréquence d'usage décroissante dans la langue. On énonce au départ, à voix haute, lentement et une seule fois, le nom générique suivi de ses cinq mots associés (exemple : "arbres", suivi de "chêne, pin, baobab, orme") ; trente minutes après (en pratique après la passation des autres tests), le sujet doit, au rappel du nom générique, écrire dans les cinq cases de la feuille réponse les cinq noms de la série dans l'ordre où ils ont été énoncés.

La cotation prend en compte les mots mémorisés et leur place (2 points par mot mémorisé et correctement placé, 1 point par mot mémorisé mais déplacé), (soit z/10). Le test comporte huit séries parallèles.

4 - Auto-questionnaire sur la forme au réveil.

C'est un questionnaire de 25 questions simples inventoriant l'état physique et (surtout) psychique du sujet au réveil. Les questions sont ordonnées dans l'ordre chronologique des états d'âme et des activités du réveil (ouvrir les yeux, se repérer, s'asseoir dans le lit, mettre pied à terre...), mais sont ventilées en fait en cinq domaines comprenant chacun cinq questions : moteur, sensoriel, lucidité, efficience intellectuelle, thymie. Il donne lieu à une note de méforme au réveil, total de 5 subtotaux, de s/25.

Ce questionnaire n'est pas un test de performance, il a été pris en compte à part, comme indice de l'évaluation subjective de la forme au réveil et il a servi à apprécier, au coup par coup, la distorsion qui peut exister au réveil entre un vécu subjectif euphorique et une efficience réelle altérée.

5 - Test des carrés type Zazzo. (Test informatisé).

C'est un test de reconnaissance de forme qui évalue l'attention sélective (et aussi le temps de réaction). Inspiré du test de barrage de Zazzo, qui était un test papier-crayon consistant à barrer le plus vite possible deux signes parmi huit signes possibles dans une feuille de deux mille signes, le test informatisé présente les signes à reconnaître un par un, successivement, au centre de l'écran. Cette présentation assure une exploration plus pure de l'attention, sans interférence de la stratégie d'anticipation visuelle sur la feuille. Les signes à reconnaître sont des carrés, agrémentés d'un trait sur leur périmètre extérieur, soit perpendiculaire au milieu d'un des quatre côtés, soit en prolongement de la diagonale d'un des quatre angles (huit possibilités). La tâche consiste à appuyer le plus vite possible soit sur la touche OUI soit sur la touche NON dès que l'on a identifié le signe apparu sur l'écran, qu'un nouveau signe vient remplacer immédiatement après la réponse.

Le programme de correction comptabilise le pourcentage d'erreurs (faux positifs et faux négatifs), le temps total de passation et le temps moyen par réponse. Il établit en outre la courbe des temps de réponse cumulés, calcule le coefficient de régularité des temps de réponse (inverse de la variance) et les indices d'apprentissage ou de fatigue pour les deux moitiés successives du test (pentes de la courbe des temps de réponse cumulés pour ces deux moitiés, enregistrés dans leurs coordonnées x et y et traités par deux transformations logarithmiques).

La multiplicité des combinaisons à deux modèles (28 possibilités) et des ordres de présentation des signes offre un très grand nombre de formes parallèles du test et évite la mise en jeu d'un effet parasite de mémorisation.

Dans la présente expérimentation, on a choisi une configuration à 200 signes .

6 -Test des barres colorées. (Test informatisé).

C'est un test de mémoire visuelle immédiate qui consiste à se remémorer, après un bref temps de présentation sur écran, une configuration de neuf barres verticales alignés horizontalement dont certaines sont blanches et d'autres teintées d'une couleur. On peut faire varier le temps de présentation et le nombre de couleurs. Dans la présente expérience, on a choisi une modalité à cinq secondes et trois couleurs.

Dans la pratique, le test est programmé en difficulté croissante (de une à huit barres colorées). Le sujet doit, le plus vite possible, donner sa réponse après disparition des couleurs (il ne subsiste alors sur l'écran que neuf barres blanches) en actionnant les touches numériques du clavier (position) et les touches lettres correspondant aux initiales des couleurs. Pour faciliter le test, on a teinté ces touches par les couleurs correspondantes : B - bleu, R - rouge, J - jaune, V - vert.

Le programme de correction enregistre chaque réponse et chaque temps de réponse. Il comptabilise les erreurs et calcule le pourcentage d'erreurs. Il calcule en outre le temps moyen par réponse, le coefficient de régularité du temps de réponse et les indices de fatigue ou d'apprentissage dans les deux moitiés successives du test.

7 - Test "taches-sons" (test informatisé).

C'est un test de charge mentale explorant à la fois l'attention, la mémoire visuelle et la mémoire auditive en situation de surcharge d'information.

Le test consiste à repérer, parmi une population de N petites taches rectangulaires de dimensions et de couleurs variables apparaissant une à une à des endroits divers de l'écran où elles subsistent (réalisant une surcharge progressive d'information) celles qui ont été précédées d'un signal composé d'un nombre variable de sons brefs. A chaque apparition d'une tache significative le programme de succession des taches est suspendu et le sujet doit répondre (par le clavier) aux deux questions "couleur de la tache" et "nombre de sons du signal".

Le programme de présentation permet de faire varier le nombre total de taches, leur vitesse de succession, le nombre de couleurs impliquées, le nombre de sons des signaux et le pourcentage de taches significatives. Dans la présente expérimentation, on a choisi une configuration à 60 taches, 5 cou-

leurs, 7 sons, 2 secondes de succession et 20 % de taches significatives.

Le programme de correction comptabilise les erreurs, calcule leurs pourcentages (erreurs sur le son et erreurs sur la couleur), calcule le temps total, le temps moyen par réponse et le coefficient de régularité des temps de réponse, ainsi que les indices d'apprentissage ou de fatigue dans les deux moitiés successives du test.

8 - Test du classement des chiffres. (test informatisé).

C'est un test de raisonnement numérique, appréciant aussi la vigilance et la concentration intellectuelle.

Il consiste à classer le plus rapidement possible, dans l'ordre croissant, des séries de chiffres présentées sur l'écran dans un ordre aléatoire. Ce n'est pas un test de mémoire, puisque les séries de chiffres restent affichées sur l'écran tout le temps de l'opération de classement (qui est effectuée par actionnement des touches numériques), mais un test de concentration et de raisonnement. Le test est assez difficile, car le sujet ne peut pas rectifier ses erreurs et il doit agir le plus vite possible.

Le programme de présentation permet de faire varier le nombre de chiffres par série et le nombre de séries à classer. Dans la présente expérimentation, on a choisi dix séries de neuf chiffres chacune.

Le programme de correction comptabilise les erreurs (une seule erreur suffit à compter la série comme "fausse"), calcule le temps total et le temps moyen par réponse, le coefficient de régularité et les indices d'apprentissage ou de fatigue dans les deux moitiés du test.

Les tests papier-crayon ont fait l'objet d'un étalonnage et d'une validation en 1969 et 1971, sur une population de mille sujets adultes de 20 à 60 ans et plusieurs échantillons (200 sujets) de patients présentant une détérioration mentale (2) (3).

Les tests informatisés ont fait l'objet d'un étalonnage et d'une validation sur diverses populations de sujets adultes (20 à 60 ans) entre 1980 et 1984 (4) (5).

En résumé, par référence aux différentes capacités mentales entrant en jeu dans la vigilance et l'efficience intellectuelle, la batterie de tests explore :

- l'attention (test papier-crayon du double barrage et test informatisé des carrés type Zazzo),
- la mémoire visuelle immédiate (test papier-crayon des damiers et test informatisé des barres colorées),
- la mémoire différée (test papier-crayon des noms génériques),
- le raisonnement numérique (test informatisé du classement de chiffres),
- l'efficience perceptivo-motrice et la mémoire en situation de surcharge d'information (test informatisé "taches-sons").

L'ordre de passation, identique pour tous les sujets, a été aménagé en fonction de considérations pratiques et d'accoutumance pour des sujets non habitués à se servir de consoles d'ordinateur (difficulté croissante pour les tests informatisés). Il a été le suivant :

1 - consignes des noms génériques
2 - damiers
3 - double barrage
4 - auto-questionnaire
5 - classement de chiffres
6 - carrés type Zazzo
7 - taches-sons
8 - barres colorées
9 - remémoration différée des cinq mots associés au nom générique.

Dispositif matériel.

Au plan matériel, nous avons utilisé un micro-ordinateur APPLE II, de 48 K de mémoire, relié à un moniteur couleur et à une imprimante. Pour faciliter la tâche de réponse, nous avons coloré les touches correspondant aux couleurs par les teintes correspondantes et marqué d'une pastille de signalisation les touches O (= OUI) et N (= NON) ainsi que les touches chiffres.

Par la suite, pour d'autres tests, nous avons élaboré un clavier-réponse simplifié spécialement adapté à l'utilisation psychométrique du micro-ordinateur.

Nous avons aussi élaboré les programmes informatiques adéquats pour :

- la présentation des consignes des tests, en courtes phrases,
- le choix de la modalité de passation et des formes parallèles,
- le déroulement interactif de la passation,
- l'enregistrement des réponses (scores et temps),
- le calcul des résultats,
- le calcul des indices (coefficient de régularité, indice d'apprentissage ou de fatigue).

IV - Résultats.

1 - Profils individuels.

Dans un premier temps, nous avons établi, pour chacun des 16 sujets, le profil individuel des résultats psychométriques obtenus à chaque test pour les passations 2 à 8 (on n'a pas pris en compte la passation à blanc n° 1, considérée comme passation d'apprentissage), en respectant l'ordre chronologique c'est-à-dire de J 4 à J 28. On a donc obtenu 16 profils, composés chacun de 16 sous-profils (un sous-profil par test) (cf. fig. 1).

En abscisse on porte les passations successives (à intervalle de 4 jours) en mentionnant à chaque fois le produit correspondant (connu en fin d'expérimentation après levée du double aveugle). A noter que la correspondance produit-ordre de passation, aléatoire, n'est pas la même pour tous les sujets. En ordonnée on porte soit le pourcentage d'erreurs, soit le temps total ou le temps moyen de

réponse (selon le test), ce qui fait que toute élévation du profil (en pourcentage d'erreurs ou en temps) traduit une baisse d'efficience ou une détérioration.

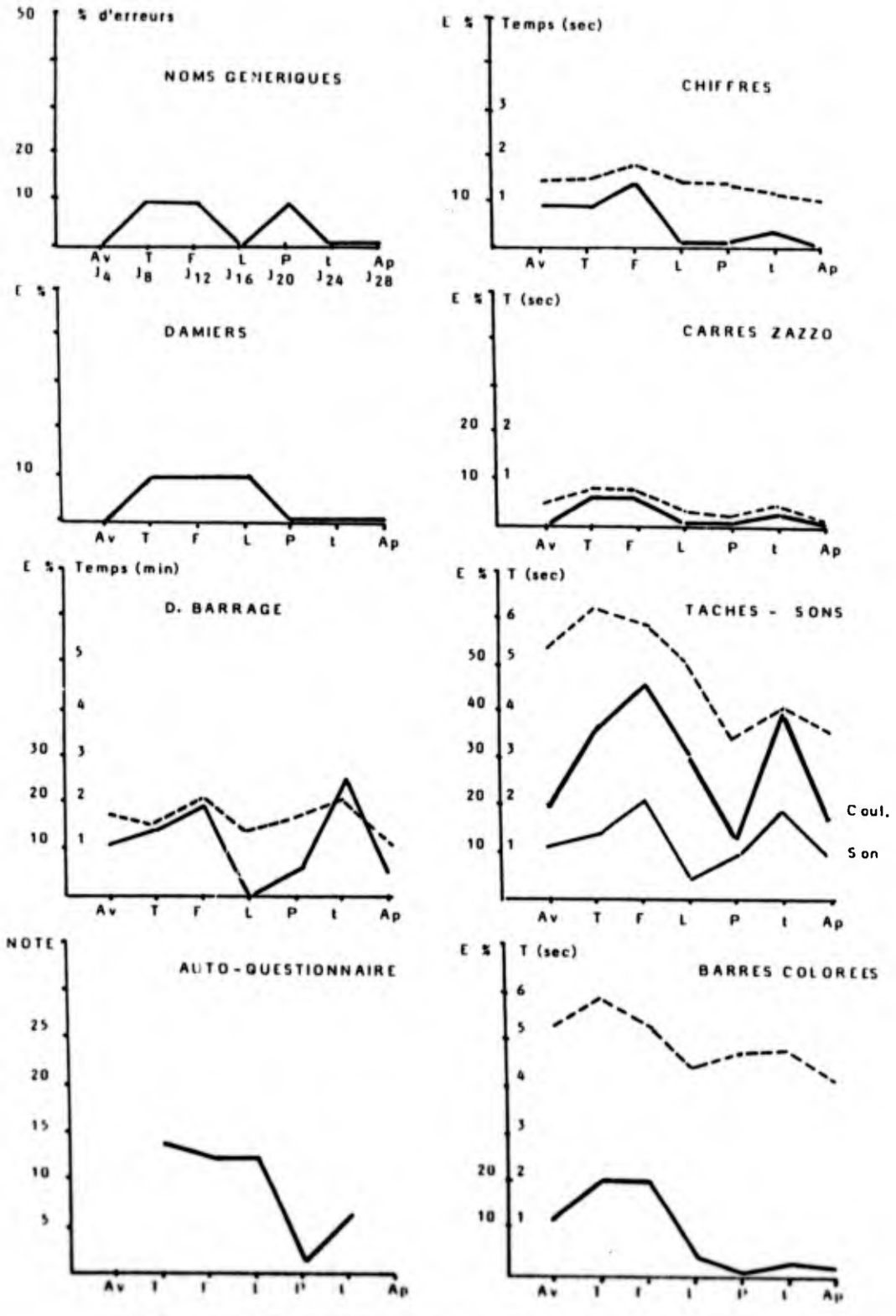

Fig 1 : Profil individuel du sujet S 1 aux huit tests _____ : scores ---------- : temps

Une fois en possession de ces 16 profils individuels, on a examiné leur pente générale, pour détecter l'existence d'un éventuel facteur à long terme qui - selon les sujets - se serait traduit par une tendance générale à améliorer les performances (abaissement progressif des courbes) ou à les détériorer (élévation progressive des courbes) indépendamment de l'action des profilés et de leur ordre de prise. Cette tendance générale serait imputable à l'accoutumance aux tests, produisant soit un effet

	PLACEBO							LOPRAZ							TRIA 0,25							TRIA 0,50							FLUNITR.						
	N. CEN	DAMIERS	D. BARRAGE	CHIFFRES	C. ZAZZO	COUL - SON	BAR. COLOR	N. CEN	DAMIERS	D. BARRAGE	CHIFFRES	C. ZAZZO	COUL - SON	BAR. COLOR	N. CEN	DAMIERS	D. BARRAGE	CHIFFRES	C. ZAZZO	COUL - SON	BAR. COLOR	N. CEN	DAMIERS	D. BARRAGE	CHIFFRES	C. ZAZZO	COUL - SON	BAR. COLOR	N. CEN	DAMIERS	D. BARRAGE	CHIFFRES	C. ZAZZO	COUL - SON	BAR. COLOR
S1	X								X				X					X			X					X	X	X	X	X	X	X	X	X	X
27													X					X			X	X	X	X	X	X	X	X			X	X		X	X
S2													X					X			X											X			X
21						X			X			X	X					X	X		X	X	X		X					X	X	X	X	X	X
S3											X													X			X		X			X			X
23		X		X					X	X	X	X		X					X		X			X	X		X		X		X	X	X	X	X
S4																X							X												
16	X		X	X		X			X	X	X					X		X					X							X	X			X	X
S5					X								X		X							X		X						X	X				
24		X			X		X					X	X	X	X	X		X			X	X		X					X	X	X			X	X
S6																								X								X	X	X	
22						X					X		X	X		X	X	X			X			X	X	X			X	X	X	X	X	X	X
S7								X			X		X	X										X		X									
21				X				X		X	X	X	X	X							X		X	X	X	X	X	X					X		
S8																						X			X	X	X		X						
20				X							X	X					X		X		X	X	X	X	X	X	X	X	X					X	X	
S9								X															X	X	X		X	X			X	X				
25			X				X	X					X			X						X	X	X	X	X	X	X		X	X			X	X	
S10								X							X			X			X				X		X	X	X	X	X	X			X	
30								X				X			X	X	X	X		X	X				X	X	X	X	X	X	X	X	X		X	
S11													X										X	X	X	X	X				X			X	X
25		X								X	X		X				X		X			X	X	X	X	X	X	X			X		X	X	X
S12																X				X	X			X	X			X				X	X		X
27			X								X		X	X		X			X	X			X	X	X	X	X	X	X		X		X	X	X
S13																						X			X	X	X	X							
23											X	X	X		X		X	X	X	X	X	X		X	X	X	X	X				X	X			X
S14									X											X	X	X		X	X	X	X	X	X	X						
26			X						X				X		X	X			X	X		X		X	X	X	X	X	X	X				X		
S15									X		X	X	X	X								X														
22		X	X	X				X	X	X	X	X	X	X		X	X					X										X		X	X	
S16																		X																		
19		X								X			X			X		X	X					X	X		X		X	X	X		X	X	X	X
Accidents Majeurs						1		3	2		3	1	4	2	2	2	2	2		4	1	5	3	8	6	6	7	6	4	3	7	6	3	5	6
TOTAL maj. + moy	2	5	5	5	2	3	2	7	8	7	11	9	16	8	6	11	11	8	6	13	5	14	11	20	19	16	18	15	13	13	20	14	13	17	18
TOTAL	1/74							15/66							13/60							41/113							34/108						

FIG. 2 : Tableau récapitulatif des accidents relevés sur les profils

d'apprentissage soit, paradoxalement, un effet de lassitude ou de désintérêt. En fait, cette tendance n'a été constatée que chez quelques sujets et très discrète par rapport aux pics et accidents traduisant l'action des produits. On peut donc l'éliminer comme facteur parasite susceptible d'interférer dans la validité des résultats. On a ensuite relevé, sur les sous-profils, tous les accidents notables en élévation sur les courbes (pics ou plateaux) traduisant une baisse d'efficience et donc - éventuellement - une action de tel ou tel produit dans le sens de la détérioration. Il s'agit là d'une méthode empirique, dépendante de l'appréciation personnelle du chercheur (qu'est-ce qui mérite d'être retenu comme un pic en élévation et qu'est-ce qui doit être considéré comme négligeable ?) et peu orthodoxe au plan de la rigueur statistique mais finalement assez conforme à la clinique et aux aléas de la passation des tests. On a aussi pu constater que, dans la plupart des cas, pour un même sujet, les accidents des sous-profils (pics ou plateaux) coïncidaient, c'est-à-dire correspondaient à telle ou telle passation et donc à tel ou tel produit.

Puis, en accordant deux points ($\overset{x}{x}$) pour une élévation importante et un point (x) pour une élévation moindre, on a construit un tableau matriciel récapitulatif de tous les accidents observés sur les sous-profils, en les référant aux produits (placebo inclus) et à chacun des sept tests de performance (le questionnaire d'auto-appréciation n'était pas un test de performance). (fig. 2)

En effectuant les totaux partiels et globaux, par sujets, par tests et par produits, on a pu faire ressortir les premières constatations empiriques ci-après :

- Il existe des différences sensibles de réactivité individuelle. Evaluée à deux points par accident important sur les courbes et à un point par accident moyen, cette réactivité se situe aux valeurs suivantes : 16, 19, 20, 21 (deux fois), 22 (deux fois), 23 (trois fois), 24, 25 (deux fois), 26, 27 (deux fois) et 30.

- La réaction spécifique à tel ou tel produit est la suivante :
  . un sujet (S 15) n'est sensible qu'au loprazolam,
  . trois sujets (S 2, S 6 et S 16) ne sont sensibles qu'au flunitrazépam,
  . un sujet (S 8) n'est sensible qu'au triazolam 0,50,
  . deux sujets (S 13 et S 14) sont sensibles au triazolam 0,25 et 0,50,
  . un sujet (S 7) est sensible au loprazolam et au triazolam 0,50,
  . quatre sujets (S 1, S 5, S 9 et S 11) sont sensibles au flunitrazépam et au triazolam 0,25 ou 0,50,
  . un sujet (S 3) est sensible au flunitrazépam, au triazolam 0,50 et au loprazolam,
  . deux sujets (S 10 et S 12) sont sensibles au flunitrazépam et au triazolam 0,25 et 0,50.

  Ce qui fait que, au plan de l'action des produits dans la population des 16 sujets :
  . la sensibilité au loprazolam apparaît trois fois,
  . la sensibilité au triazolam 0,25 apparaît six fois,
  . la sensibilité au triazolam 0,50 apparaît dix fois,
  . la sensibilité au flunitrazépam apparaît dix fois.

Le relevé des accidents importants (2 points) et moyens (1 point) par produit donne les résultats suivants :

Placebo : 1 accident important et 22 accidents moyens = 24 points
Loprazolam : 15 accidents importants et 36 accidents moyens = 66 points
Triazolam 0,25 : 13 accidents importants et 34 accidents moyens = 60 points
Triazolam 0,50 : 41 accidents importants et 31 accidents moyens = 113 points
Flunitrazépam : 34 accidents importants et 37 accidents moyens = 108 points

Capacités	Tests	LOPRAZ 1	TRIA 0,25	TRIA 0,50	FLUNIT 1
Attention	Double barrage	7	11	20	20
	Carrés zazzo	9	6	6	13
Mémoire immédiate	Damiers	8	11	11	13
	Barres colorées	8	5	15	18
Mémoire différée	Noms génériques	7	6	15	13
Raisonnement	Class. chiffres	11	8	19	14
Tâche complexe	Taches - sons	16	13	18	17
	Nombre total d'accidents	66	60	113	108

Fig 3 : Profil d'action de chaque produit sur la détérioration des différentes capacités mentales

Le profil d'action de chaque produit peut être déterminé en fonction de l'importance élective de la détérioration qu'il produit aux différents tests, et donc sur les différentes capacités mentales (voir fig. 3).

On en retiendra les tendances suivantes :
. Le triazolam 0,50 et le flunitrazépam altèrent l'attention deux à trois fois plus (selon les tests) que le loprazolam et le triazolam 0,25.
. Le triazolam 0,50 et le flunitrazépam altèrent la mémoire immédiate et la mémoire différée deux à trois fois plus que le loprazolam et le triazolam 0,25.
. Par contre, pour les fonctions supérieures (raisonnement et tâches complexes), cette différence, bien que notable, tend à se réduire.

Exploitation statistique.

On a ensuite entré en ordinateur tous les résultats obtenus par les 16 sujets aux 7 tests d'efficience pour les 7 passations (en prenant en compte, cette fois, les passations par produit et non plus par ordre chronologique), on les a disposés en tableaux à double entrée (sujets en rangées, produits ou passation en colonnes) et on a calculé les moyennes, les écarts-types, les erreurs standards sur les moyen-

nes et les moyennes réduites.On a ainsi disposé de vingt-cinq tableaux de données statistiques : 8 tableaux pour les scores (puisque le test "taches-sons" donne lieu à deux scores, un pour la couleur et un pour le son), cinq tableaux pour les temps (quatre pour les tests informatisés et un pour le double barrage), quatre tableaux pour les coefficients de régularité et huit tableaux pour les indices "apprentissage" ou "fatigue" des tests informatisés.

On a procédé, pour chaque tableau de résultat, à une analyse de variance à deux facteurs contrôlés (F de Snedecor) pour détecter une différence significative entre les colonnes (donc entre les passations ou produits), puis à l'identification des causes de ces différences par la méthode de Newman-Keuls (comparaison des moyennes réduites par référence à la table du range studentisé). Le relevé de ces comparaisons a donné lieu à l'établissement de vingt-cinq tableaux à double entrée où sont évaluées deux à deux les différences entre les moyennes réduites des sept passations (cf. l'exemple en fig. 4). Enfin, dans un tableau récapitulatif (fig. 5), on a totalisé les "distances" entre passations, en attribuant 1, 2 ou 3 points selon le degré de significativité (05, 01, ou 001).

Ce qui a permis de constater les résultats suivants :

. En prenant comme référence l'efficience psychométrique de base (c'est-à-dire celle des passations "à blanc" P_2 et P_8) il existe une différence très significative (+++) entre ces efficiences et celle des passations sous flunitrazépam et triazolam 0,50 ; par contre, la différence entre ces efficiences et celle sous loprazolam et triazolam 0,25 est peu significative (x) ou non significative (NS).

. En prenant comme référence l'efficience sous placebo, il existe une différence moyennement significative (xx) entre cette efficience et les efficiences sous flunitrazépam et triazolam 0,50 ; une différence peu significative (x) entre cette efficience et les efficiences sous loprazolam et triazolam 0,25 ; pas de différence (NS) entre l'efficience placebo et les efficiences des passations "à blanc".

. La totalisation des "distances" afférentes à chaque produit permet de les classer en trois groupes :

- le groupe "fort" (flunitrazépam et triazolam 0,50), qui, avec 53 points, produit manifestement une détérioration de l'efficience psychométrique,
- le groupe "faible" (triazolam 0,25, 8 points, et loprazolam, 5 points) a une effet d'altération de l'efficience beaucoup plus discret,
- le groupe "nul" (placebo, 0 point) à effet nul sur l'efficience psychométrique.

Enfin, on a terminé l'analyse statistique des résultats par la comparaison des efficiences sous chaque produit entre le groupe des sujets jeunes (20-25 ans) et le groupe des sujets mûrs (30-35 ans). La différence, en défaveur des sujets mûrs (plus détériorés et plus sensibles à l'effet des produits) n'atteint pas le seuil de significativité.

CONCLUSION

Pour détecter et évaluer les effets résiduels des benzodiazépines hypnotiques sur la vigilance et l'efficience mentale au réveil, nous avons effectué une expérimentation sur 16 sujets militaires (8 jeunes et 8 plus âgés) prenant tous en double aveugle le soir à quatre jours d'intervalle et dans un ordre aléatoire différent pour chaque sujet les produits suivants : placebo, loprazolam 1 mg, triazolam 0,25 mg, triazolam 0,50 mg et flunitrazépam 1 mg.

Pour apprécier l'efficience au réveil, nous avons utilisé une batterie de huit tests psychométriques (un questionnaire d'autoévaluation, trois tests d'efficience papier-crayon et trois tests d'efficience informatisés) adaptée à détecter et apprécier les variations infra-cliniques et à explorer non seulement la performance finale mais aussi le déroulement de la passation.

Au plan méthodologique on a procédé d'abord à l'examen empirique des profils individuels et à la comptabilité des pics de variation, puis à une exploitation statistique plus rigoureuse des résultats par analyse de variance et méthode de hiérarchisation de Newman - Keuls.

Les résultats - aussi bien dans la démarche empirique que dans l'étude statistique - sont les suivants :

1 - toutes les benzodiazépines hypnotiques utilisées, aux dosages indiqués, ont un effet résiduel de détérioration de l'efficience mentale au réveil ;

2 - cet effet est plus ou moins important en fonction des produits et (en ce qui concerne le triazolam) en fonction des dosages ;

3 - cet effet est plus ou moins important, aussi, en fonction des individus (il y a des individus plus sensibles aux effets des benzodiazépines ou même de telle ou telle benzodiazépine).

4 - cet effet semble s'exercer davantage sur les individus plus âgés ;

5 - cet effet s'exerce plus sur les fonctions mentales supérieures (raisonnement et tâche complexe en surcharge d'information) que sur les fonctions mentales élémentaires d'attention et de mémoire immédiate ;

6 - pour plusieurs tests informatisés et pour certains produits et certains sujets, l'effet de détérioration a été révélé plus par le calcul de la régularité du temps de réponse et de l'indice de fatigue que par le niveau de performance finale, ce qui tend à montrer que l'on peut parfois parvenir à maintenir son niveau de performance apparent en sacrifiant le temps de réaction ou la régularité de la performance (détérioration infra-clinique) ;

7 - un examen approfondi tend à faire apparaître des "profils différentiels" de produit : ainsi le loprazolam altérerait seulement l'efficience des fonctions supérieures (tâches complexes) ; le triazolam 0,25 altérerait aussi cette efficience supérieure (dans un degré moindre) mais altérerait aussi l'attention et la mémoire visuelle immédiate ; le triazolam 0,50 altérerait plus nettement l'attention, les fonctions supérieures et (dans une moindre mesure) la mémoire ; enfin, le flunitrazépam altérerait l'attention, la mémoire immédiate et l'efficience en tâche complexe.

Il convient toutefois de restreindre ces conclusions aux limites de la situation expérimentale : la situation de laboratoire est loin de la situation concrète sur le terrain et notre batterie de tests ne recouvre pas exactement les capacités requises dans toutes les missions opérationnelles.

Malgré tout, nos résultats confirment les observations cliniques empiriques de la prescription des benzodiazépines hypnotiques. Nous tendons à admettre qu'aucune benzodiazépine n'est "innocente" en regard des effets secondaires ou résiduels sur la vigilance et l'efficience, à court et long terme.

Ceci étant dit : les besoins opérationnels sont là, l'efficience de certaines missions n'implique pas les fines variations infra-cliniques (encore qu'il convient de se méfier du risque de détérioration de l'efficience si l'effort demandé est plus intense ou plus prolongé que prévu) et - dans la pharmacopée existante - les benzodiazépines hypnotiques peuvent rendre service. Encore faut-il alors, compte tenu de ce que nous avons observé, choisir ses produits, choisir ses doses et choisir ses hommes.

	Avant	Après	Placebo	Loprazolam	Triazolam 0,25	Triazolam 0,50	Flunitrazépam
Avant		NS	NS	NS	++	+++	+++
Après			NS	NS	+	++	++
Placebo				NS	+	++	++
Loprazolam					NS	+	+
Triazolam 0,25						NS	NS
Triazolam 0,50							NS
Flunitrazépam							

Tableau 4 – Évaluation des différences entre moyennes réduites pour le coefficient de régularité au test d'attention des carrés type Zazzo.

NS = non significatif, + = significatif .05, + + = significatif .01, + + + = significatif .001

	Avant	Après	Placebo	Loprazolam	Triazolam 0,25	Triazolam 0,50	Flunitrazépam
Avant		– 3	0	1	3	16	11
Après			0	2	2	15	17
Placebo				2	2	10	14
Loprazolam					1	10	7
Triazolam 0,25						2	4
Triazolam 0,50							0
Flunitrazépam							
TOTAL		– 3	0	5	8	53	53

Tableau 5 – Tableau récapitulatif des « distances » entre passations.

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12 - PARROTT A.C. et DAVIES S. - Effects of a 1-5 benzodiazepine upon performance in an experimental stress situation - Psychopharmacology, 1983, 79, 367-369.

TEST DES SERIES GENERIQUES
(mémoire différée)

Série 1. ARBRES	- chêne,	pin,	hêtre,	baobab,	orme
Série 2. FLEURS	- rose,	tulipe,	myosotis,	glaïeul,	gardenia
Série 3. FRUITS	- pomme,	cerise,	ananas,	myrtille,	coing
Série 4. LEGUMES	- tomate,	choux,	poireaux,	salsifi,	fenouil
Série 5. CHIENS	- caniche,	bouledogue,	basset,	épagneul,	dalmatien
Série 6. ANIMAUX DOMESTIQUES	- cheval,	boeuf,	bélier,	buffle,	mulet
Série 7. ANIMAUX SAUVAGES	- lion,	léopard,	zébu,	hyène,	tapir
Série 8. OISEAUX	- moineau,	rouge-gorge,	mésange,	chardonneret,	passereau
Série 9. POISSONS	- brochet,	gardon,	piranâ,	brême,	verron
Série 10. OUTILS	- marteau,	scie,	tenailles,	lime,	alène

ANNEXE I - Test des noms génériques.

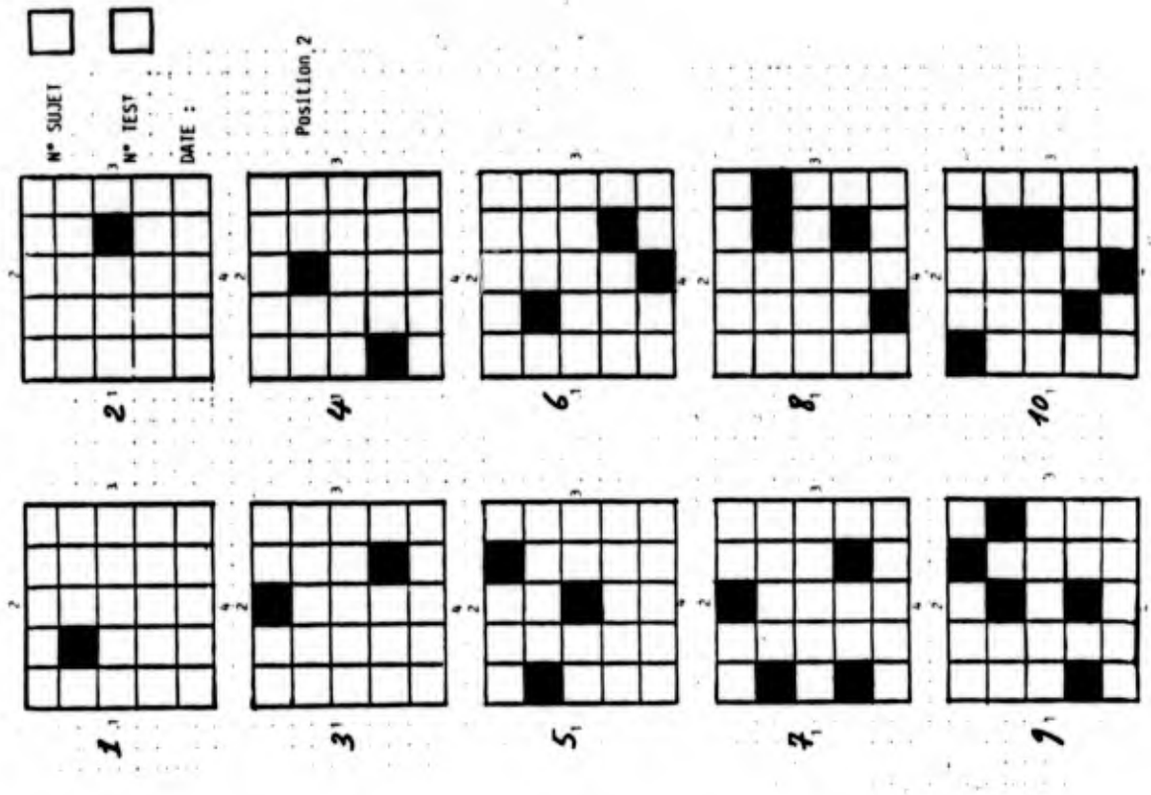
TEST DU DOUBLE BARRAGE

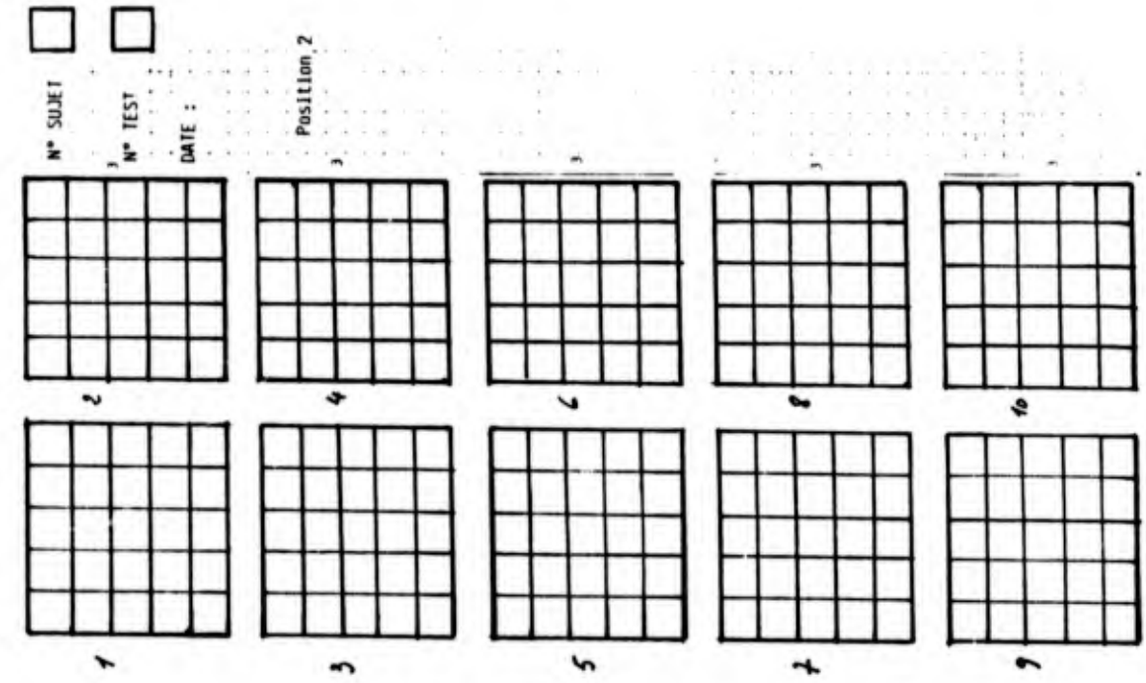
0 V 2 V ? N W Z N V K V P 4 A U 3 U X O S 5 N V 7 U U V O Y O O C V W V L U O M
N M O 1 V T W B M U D N F V N D O U U H S O R U U O E U M 9 M P W V V O 6 V U L
N N M O A V U V O H M S U T M W O M 3 O M 8 S O R S 5 V V N Z O S O U 7 S U M W
O M O U V N E N U S V O B U O C V O 5 U S U O 2 L P V N O Y W 2 S Y O S S O N V
S U 6 O M V S 8 8 O U U 1 V S O F U U R O 4 9 W O 3 V N E O 3 U W S N O M K N W
S S U C W O U M O S H U S M N O X V V D W W 6 V U S O B O X U O N O W N U N N M
M N 9 N 4 O Z U S O S V 7 N 1 U M V O U Y 4 N Z O U O T S S O 1 U B O N M F M N
U W K N S O 3 N V X W S N N D N O 2 N N P U N N 5 O V S M N W S O N O 1 M N U O
O U S N O D N O M S M E U M R U V M E O W U N U H W N N 7 W N 8 W N O N M W O W
W S T O N M C O S O U C O V U U 9 V V M U 6 V V N O 6 M M T N S L S 9 S K O U M
N U 3 U O U S N B M O 2 U V O U Y U O M N A O N A V N S M M F O W O U N O M O 4
N U M P X M U O U M W R O U S N U O H N L Z U O 1 W N M E N U M U O 5 L 5 N N O
M O S W V 6 U N O O M W 8 N M K M O C O M O T O U D V V S V 3 U N N U W N U O U
W N M 4 7 O N 7 N O 2 N W K N O 9 M W 1 O W M O N V E V O N B Y U B N O N W U U
U V M M U U S N 6 S U V O U F O M W O X W O U 5 N W O U N M O V U W V N N N O V
N O O V A O M W O D U M O H U O R O 4 O U H O S N O V 2 N O T U S U C O N Z O V
M P 6 V S O O Z N U S V U M W N B N W O 1 N O W N E M N D L V O N M O V N S W N
O S M M U O Y O S 3 N K U 9 O U M O S S O 7 C O O W U O S U O 8 S O X W O S U M
N S U U M O W 5 U S O S U A N P N F O M M U S V U F N 4 N T U O V N W O N W N O
U 9 K V S V W U O M V 5 U M O S M N B O S V X V W U 2 N E N N U N S H O N U M M
M O S R W S T S M 7 O S V R N W V W D U L U O P M O O U N U A P U M W 8 V N N O
O A V Y V U W S O V X W 3 W M H O V V S L O M C O U 6 V M 2 N O M W V U O L Z N
V S V 4 O V Z N W M K N O O M U V U 8 U 7 S S U 9 V O W F S U V R U W N O O N M
M O V E O U 8 W N X O S W 6 V N 3 O N Y V 1 L H O U B N D V 2 O N A W N W O U N
O V 8 W T W Z U F O V M 4 C N N A O U K N W N 5 O P O O V Y N R N 9 U 7 O U W N

N° : SCORE :

DATE : TEMPS :

ANNEXE II - Test du double barrage
Les huit séries parallèles sont :
A2 - B3 - C4 - D5 - E6 - F7 - H8 - K9.





ANNEXE III - Test des damiers
Ici la forme parallèle en position 2
(face 2 présentée en haut)

QUESTIONNAIRE SUR L'ETAT PHYSIQUE ET PSYCHIQUE AU REVEIL

Cochez d'une croix les cases-réponses qui correspondent à votre état.

1 — En ouvrant les yeux ce matin, j'ai mis plus de temps que d'habitude à me repérer dans l'espace et le temps.	☐ L1
2 — Une fois réveillé ce matin, je suis resté plus longtemps dans mon lit avant de mettre le pied au sol.	☐ M1
3 — Au réveil, ce matin, ma vision était un peu floue.	☐ S1
4 — En m'asseyant dans mon lit ce matin, j'ai ressenti quelques vertiges.	☐ S2
5 — Au réveil ce matin, j'avais un peu mal à la tête.	☐ S3
6 — Au réveil ce matin, j'avais la bouche sèche.	☐ S4
7 — Au réveil ce matin, je ressentais de la fatigue physique.	☐ M2
8 — Ce matin, au réveil, je me sentais triste.	☐ T1
9 — Ce matin, mes premiers gestes étaient maladroits.	☐ M3
10 — Ce matin, au réveil, ma voix était pâteuse et embrouillée.	☐ L2
11 — Ce matin, au petit déjeuner, j'avais moins d'appétit que d'habitude.	☐ S5
12 — Depuis ce matin, je suis inquiet et j'appréhende l'avenir.	☐ T2
13 — Ce matin, je me sens moins lucide que d'habitude.	☐ L3
14 — Ce matin, mes réflexes sont moins rapides que d'habitude.	☐ M4
15 — Ce matin, je réponds moins vite quand on m'appelle.	☐ L4
16 — Depuis ce matin, mon activité motrice est ralentie.	☐ M5
17 — Depuis ce matin, j'ai du mal à fixer mon attention.	☐ L5
18 — Ce matin, je manque de dynamisme.	☐ T3
19 — Ce matin, j'ai moins de vélocité d'esprit.	☐ I1
20 — Ce matin, j'avais des difficultés pour me souvenir de ce que je devais faire aujourd'hui.	☐ I2
21 — Ce matin, je comprends plus difficilement les questions.	☐ I3
22 — Ce matin, j'ai du mal à me concentrer.	☐ I4
23 — Ce matin, ma capacité d'évaluation et de jugement est plus indécise que d'habitude.	☐ I5
24 — Ce matin, je me sens irritable.	☐ T4
25 — Ce matin, je n'ai pas envie de parler avec les autres.	☐ T5

— Lucidité:
— Sensoriel:
— Moteur:
— Intellectuel:
— Thymique:

Total Général:

No. Date:

ANNEXE IV — Le questionnaire sur la forme au réveil.

SEDATING AND NONSEDATING SLEEPING AIDS IN AIR OPERATIONS

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SUMMARY

Both sedating and nonsedating sleeping aids may be appropriate for use in specific operational environments to promote sleep and permit efficient utilization of rest periods. "Sedating" agents, such as the benzodiazepine triazolam, produce an "impairment window" which is a period of time post-administration when performance and responsivity during sleep are impaired. "Nonsedating" agents, such as the amino acid l-tryptophan, enhance sleep but do not alter performance or responsivity at any time postadministration. In a field trial of use of l-tryptophan in U. S. Marines airlifted from California to Okinawa, l-tryptophan increased total sleep time the first night after arrival. This sleep enhancement was associated with significantly faster reaction times the next day, sparing of short-term memory from "jet-lag" effects, and more rapid recovery of reaction time over the first three days after arrival. Which type of agent to use in support of an air operation will be determined by the nature of the environments in which rest periods will occur and the duration of scheduled sleep times.

The conduct of military air operations frequently involves transits across multiple time zones, altered work-rest schedules, and sustained performance under conditions of sleep loss. Over the years, the Behavioral Psychopharmacology Department of the Naval Health Research Center (NHRC) has focused on identifying the effects of these mission factors on human performance and has emphasized evaluation of sleeping aids for use in operational settings to promote sleep and permit efficient utilization of rest periods. Our research on sleeping aids is a component of a major research program designed to develop psychopharmacological techniques to enhance and maintain human performance. The approach and philosophy behind this research program were presented at an earlier DRG symposium (1).

Our laboratory has carefully evaluated the suitability for operational use of the short half-life benzodiazepine triazolam (Halcion®) and the amino acid l-tryptophan, which are, respectively, sedating and nonsedating sleeping aids. From our point of view, the term "sedating sleeping aids" has a data-based definition--it is applied to those agents which, in addition to enhancing sleep through some pharmacological mechanism, produce measurable performance decrements and alter responsivity during sleep for some time period postadministration. This time window can be delineated in the research laboratory by repeated sampling of performance and arousal threshold, according to a standard research protocol. Conversely, "nonsedating" agents enhance sleep but do so without producing an "impairment window", as shown by performance and arousal threshold data which are not statistically different from placebo values.

In recent years, we have conducted several laboratory studies of triazolam (2, 3, 4, 5, 6). Use of triazolam at the .5 mg dose was found to be associated with performance impairment up to 5 hours postadministration, anterograde amnesia, and elevated arousal thresholds during sleep (2). The lower .25 mg dose had adequate hypnotic efficacy and was found to produce a smaller but significant performance decrement lasting approximately 4 hours after administration (3). We recently reported that responsivity to a smoke detector alarm sounded during sleep was strikingly reduced after triazolam administration at bedtime (4). These changes in performance and responsivity during sleep are presumed to be a consequence of the nonspecific CNS depressant effects of benzodiazepine-hypnotics. Depending upon the nature of the operational environment and the mission demands, the acute effects of a short-acting benzodiazepine like triazolam may or may not be problematic: if personnel are scheduled for rest in safe locations with little probability that they will be called back to duty before the dose wears off, then agents such as triazolam may be excellent choices for operational use because of their rapid onset of action and exceptional efficacy in short-term administration. However, during the effective phase of drug action, personnel would be difficult to arouse and would perform more poorly on reaction time, cognitive, and memory tasks up to 5 hours after drug use.

Because many missions require continuous readiness and are unpredictable in terms of scheduling work and rest periods, our laboratory has also investigated the nonsedating sleeping aid, l-tryptophan (7, 8, 9, 10). L-tryptophan was considered to be appropriate for use in military operations because these laboratory studies had demonstrated that it did not impair performance at any time postadministration. We and other authors have suggested that its sleep-promoting action is mediated by a serotonergic deactivation of the awake state, thus establishing a preparatory relaxation which permits more rapid sleep onset. This mechanism is nonsedating, as shown by normal task performance, intact

memory systems, and unaltered arousal threshold during the effective time period of action (8).

An air operation of considerable interest to the U. S. Marines, as well as to other services, is the airlift of large numbers of ground forces from the continental United States to distant locations. Rapid deployment across multiple time zones raises the operational issue of the consequences of the so-called "jet-lag syndrome" on military readiness. Jet-lag effects are hypothesized to result from at least three causes: sleep loss, the discrepancy between environmental and internal clocks, and circadian desynchronosis. (For a discussion of these factors, see (11)). In the following report, the results of a field trial of the efficacy of l-tryptophan in reducing the sleep-loss component of the jet-lag syndrome are described.

L-tryptophan Field Trial

The U. S. Marine Corps, in its unit deployment concept, currently airlifts whole battalions from Camp Pendleton, California (located approximately 30 miles north of San Diego), to Okinawa, Japan, for 6-month training missions. In a given week, two 747 flights transit from San Diego to Okinawa, and, during the same week, two flights return from Okinawa carrying a second battalion home. This study was conducted on the first westbound flight from San Diego to Okinawa during one of these week-long air operations. The westbound flight is approximately 15 hours air time plus a 2-hour stop in Anchorage, Alaska. Local time in Okinawa is 17 hours ahead of California Pacific Standard Time (PST). In this study, data were obtained before, during, and after the flight to assess acute jet-lag effects and to evaluate the sleep-enhancing efficacy of l-tryptophan in the field.

METHOD

Subjects

Subjects were U. S. Marines stationed at Camp Pendleton, California, who were scheduled for deployment to Okinawa, Japan. Pilot data were collected from 27 Marine volunteers from the 1st Battalion, 5th Marine Division (1/5) (mean age 21.7 $\pm$ 3.2 years). The operational trial was conducted with 51 Marine volunteers from the 1st Battalion, 7th Marine Division (1/7) (mean age 21.0 $\pm$ 2.2 years).

Procedure

The testing schedule for the operational trial is summarized in Table 1. Baseline data were collected 2 weeks prior to deployment on 3 consecutive days (B1, B2, and B3) at 0900 and 1500. On B3, in addition to the 0900 and 1500 batteries, an evening test battery was conducted at 2100. Also on B3, subjects were required to remain awake after the evening test battery until after another battery was conducted at 0300. The 4 test batteries scheduled on B3 provided comparison data for the day of the flight (F). Two days of preflight data (P1, P2) were collected at 0900 and 1500. During flight, only subjective measures and oral temperature were obtained. Arrival at Okinawa was at 1730 local time. An evening test battery was conducted at 2200. Testing on the first 2 full days (O1 and O2) in Okinawa was at 0900, 1500, and 2100. The study ended at 0800 on the third morning.

Batteries 1-12 were conducted in the battalion mess hall at Camp Pendleton. Batteries 13-15 were conducted aboard the aircraft. Batteries 16-23 were conducted in a classroom at Camp Hansen in Okinawa.

Target shooting performance was assessed one week prior to departure and on O1. Both target shooting sessions occurred at 0800 local time. Stationary targets were used. The target consisted of 3 silhouettes. Subjects were allowed one practice round on the left and right silhouette and permitted to adjust their weapon sights. Then, each subject was allowed 8 rounds on the center silhouette. Accuracy was scored using a bull's-eye scoring system with a total possible accuracy score of 40 points. Each subject used his own M16 rifle on both days. A total of 45 subjects provided target scoring data in both locations.

L-tryptophan 2 g or placebo was administered en route after reboarding at Anchorage and on the first 3 nights in Okinawa at approximately 2200, following the evening test batteries. To maximize sleep during flight, environmental interventions included timing of meals and other inflight activities, avoiding caffeinated beverages, and control of cabin lighting.

Performance and Subjective Mood Measures

Performance measures included a test of reaction time, the Wilkinson 4-Choice Reaction Time Test (RT) (12); a decoding task, the Digit Symbol Substitution Test (DSST) (13); a test of short-term memory, the Williams Word Memory Test (STM) (14); and a test involving math calculations, the Wilkinson Addition Test (AT) (15, 16). All tests chosen were known to be sensitive to sleep deprivation and to drug effects.

Subjective reports of mood were obtained through use of Analogue Mood Scales (AMS) which are a paper-and-pencil version of the computerized Visual Analogue Scales (VAS)

developed by Monk and co-workers (17), the Profile of Mood States (POMS) (18), and the Stanford Sleepiness Scale (SSS) (19).

Table 1. TEST SCHEDULE

Battery	Study Day	San Diego Time	Okinawa Time
1	B1[1]	Mon 0900	
2	B1	Mon 1500	
3	B2	Tue 0900	
4	B2	Tue 1500	
5	B3	Wed 0900	
6	B3	Wed 1500	
7	B3	Wed 2100	
8	B3	Thu 0300	
	(two weeks intervening time)		
9	P1[2]	Mon 0900	
10	P1	Mon 1500	
11	P2	Tue 0900	
12[6]	P2	Tue 1500	
13[6]	F[3]	Wed 0900[5]	
14[6]	F	Wed 1500[5]	
15[7]	F	Wed 2100[5]	
16[7]	F		Thu 2100[5]
17	O1[4]		Fri 0900[5]
18[7]	O1		Fri 1500
19[7]	O1		Fri 2100
20	O2		Sat 0900
21[7]	O2		Sat 1500
22[6]	O2		Sat 2100
23[6]	O3		Sun 0800

[1] "B" indicates baseline days, 2 weeks prior to departure week.
[2] "P" indicates days immediately prior to the flight day.
[3] "F" indicates day of the flight.
[4] "O" indicates days immediately following the day of flight.
[5] Battery was delayed due to other requirements (see text).
[6] Subjective measures and oral temperature only were obtained.
[7] L-tryptophan 2 grams administered at the conclusion of the test battery.

Physiological Monitoring

Twelve subjects wore devices for ambulatory monitoring of physiological processes. We used Medilog 9-channel recorders available from Oxford Medilog, Inc. The following physiological parameters were recorded: Left/right EOG, C4 referred to A1, C3 referred to A2, O1 referred to A2, skin temperature from an ancillary placement, EKG from two chest electrodes, and chest impedance. In addition, a time code and an event marker channel were used. Medilog subjects wore the devices continually during waking and during sleep. Cassette tapes and batteries were changed once every 24 hours. For baseline data collection, Medilogs were applied and recordings begun on B1 and removed after the 0300 test session on B3. During the week of flight, Medilog electrodes were attached and recordings begun two days before the flight and Medilogs were removed after the 23rd test battery at the end of the study. Medilog tapes were later played back on the system scanner and scored for the presence of waking or sleep (Stages 2, 3, 4 or REM) by human scorers. In this report, only the results of analysis of the EEG for total sleep time is described.

Statistical Analyses

A lengthy description of the statistical procedures employed and a detailed summary of results are presented in an NHRC Center Report (11) which is available by request from the senior author. Only an overview of the statistical procedures is presented here.

One approach to assessment of acute jet-lag effects was to measure and compare data for the same time of day at Camp Pendleton and at Okinawa. Test batteries were scheduled at 0900, 1500, and 2100 on B3 to provide baseline data for comparison with Okinawa data for the same time of day. These comparisons held local time (LT) of day constant and provided information about what kinds of jet-lag effects are to be expected if activities are scheduled according to the local time at destination. Statistically, effects were evaluated by comparing data for B3, O1, and O2 at 0900, 1500 and 2100 LT by ANOVA for repeated measures. Post hoc t-tests were used to isolate sources of significant F values.

A second statistical approach held biological time (BT) of day constant. This approach was used to determine the source of performance and mood changes that were found through the LT approach. The question asked in this approach was whether performance and mood measures were still locked to PST (biological time) and for how long after arrival. Our study design was structured to permit us to compare Okinawa data with Camp Pendleton data that was within an hour of the identical BT as follows: comparisons for the 0900 O1 and O2 batteries were made with the 1600 battery data from B3, the 1500 O1 and O2 batteries with the 2100 B3 data, and the 2100 O1 and O2 batteries with the 0300 battery from B3.

RESULTS

Sleep Management

L-tryptophan subjects obtained significantly more sleep on the first night in Okinawa compared to placebo subjects (274.5 ± 19.9 minutes versus 222.3 ± 44.8 minutes, $t = 2.16$, $p<.0314$). Total nocturnal sleep time was not enhanced on the following 2 nights. En route, control of the aircraft environment dramatically increased sleep compared to total sleep time measured in the pilot study. Pilot study Medilog subjects only obtained 120.0 ± 72 minutes sleep aboard the aircraft. The range was 16 minutes of sleep in one subject to a maximum of 3 hours 52 minutes in another. Total sleep time during the operational trial was 291.3 ± 79.2 minutes for placebo subjects and 324.3 ± 145.9 minutes for l-tryptophan subjects. This 33-minute difference in total sleep time between the 2 groups was not statistically significant. The range of sleep times was 2 to 7 hours.

Acute Effects of Flight

Upon arrival, the l-tryptophan subjects had higher mean self-reported alertness (44.7 ± 28.1 versus 31.3 ± 14.4, $t(47) = 2.09$, $p<.0425$), and a more positive mean rating of overall mood (44.4 ± 23.2 versus 31.5 ± 17.2, $t(47) = 2.20$, $p<.0327$) on the AMS. There were no performance differences between the two treatment groups upon arrival.

To determine the acute effects of flight upon performance over all subjects, battery 16 performance data were compared with battery 7 data and, separately, with battery 8 data using t-tests for correlated means. The comparisons with battery 7 provide a LT analysis and, with battery 8, a BT analysis. DSST showed essentially no decrement upon arrival. STM data suggested some slight impairment upon arrival but, comparisons of battery 16 data with battery 7 and battery 8 data showed no statistically significant differences. For AT, performance upon arrival resembled battery 8 performance and, in fact, differed significantly from battery 7. For RT, performance upon arrival was significantly slower than both battery 7 and battery 8 mean reaction times.

Evaluation of the acute effects of flight on subjective mood proceeded similarly. All t-test comparisons between battery 7 and battery 16 were highly significant. Overall, there were fewer significant differences between subjective mood upon arrival and subjective mood reported at 0300 on B3 at Camp Pendleton. Notably, reported alertness, effort required, weariness, sleepiness, and fatigue were similar upon arrival at 2200 to those at 0300 LT at Camp Pendleton. Measures which may reflect more the psychosocial difficulties encountered upon arrival including customs, a drug information lecture, and a rather long bus ride to Camp Hansen, were significantly worse than battery 8 measures. These reports included being more sad, more tense, less calm, having a poorer overall mood, and more depression and anger.

Performance Measures

Mean RT data for the l-tryptophan and placebo groups are presented in Figure 1. L-tryptophan subjects had significantly faster reaction times than placebo subjects at 2100 on O1.

Figures 2a and b present RT data for 0900, 1500, and 2100 on B3, O1, and O2 for each treatment group separately. These figures show that the l-tryptophan group's mean RTs show little change over time, while the placebo group showed a slowing at 0900 on O1 as well as at 2100 on O2.

Mean STM data for all performance batteries are presented in Figure 3. The LT analysis showed a significant day-by-treatment group interaction which was due to the fact that, compared to baseline, overall performance in the l-tryptophan group did not decline on O1 and O2, while performance in the placebo group showed a within-group impairment on both days.

As can be seen in Figures 4a and b, in the l-tryptophan group, the evening decrement in STM performance was not present on O1 but did show up on O2. The placebo group curves for O1 and O2 were highly similar to each other, and the evening decrement was present on both days.

The other performance measures AT, DSST, and target shooting accuracy showed jet-lag effects in the LT analyses, but there were no treatment-group differences.

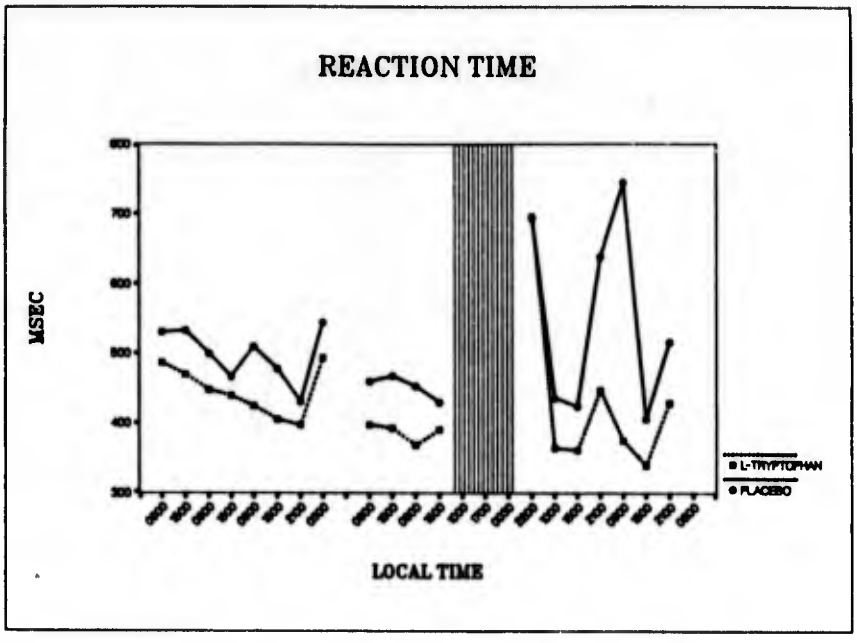
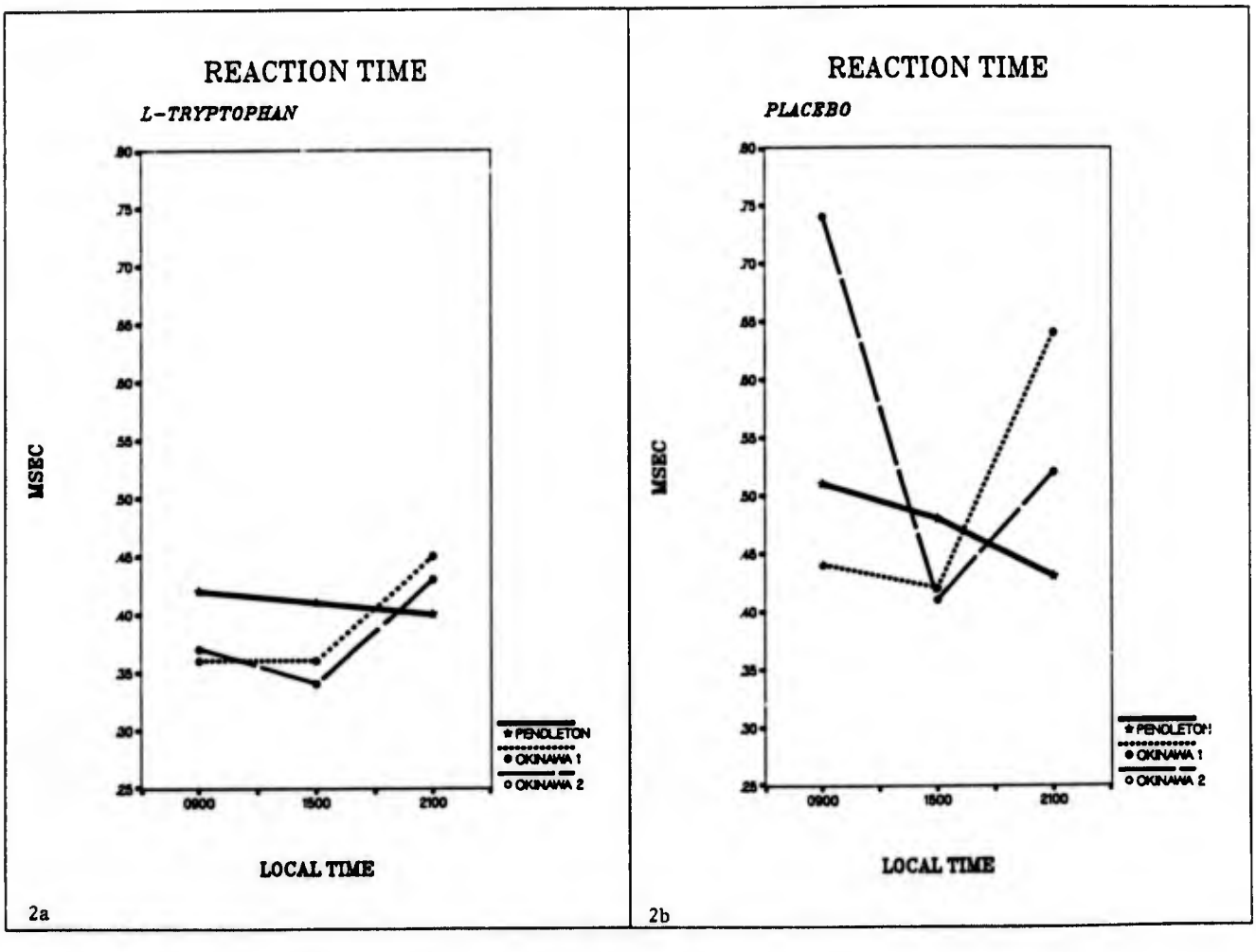


Figure 1. Mean reaction time (RT) on the 4-choice Reaction Time Test for the l-tryptophan and placebo groups separately for all test sessions.



Figures 2a & b. Mean reaction time (RT) on the 4-choice Reaction Time Test at 0900, 1500, and 2100 on study days B3, O1, and O2 for l-tryptophan and placebo groups, separately.

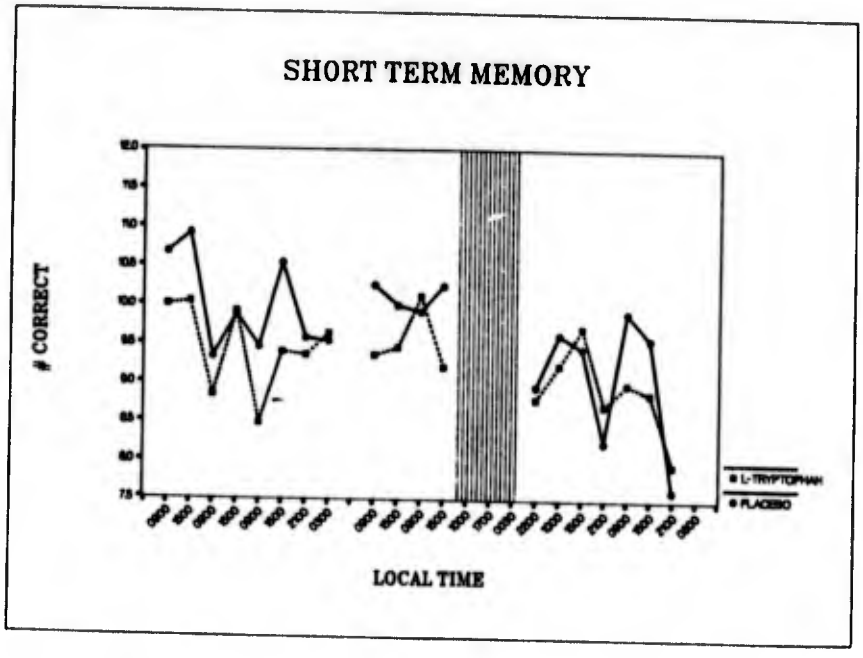
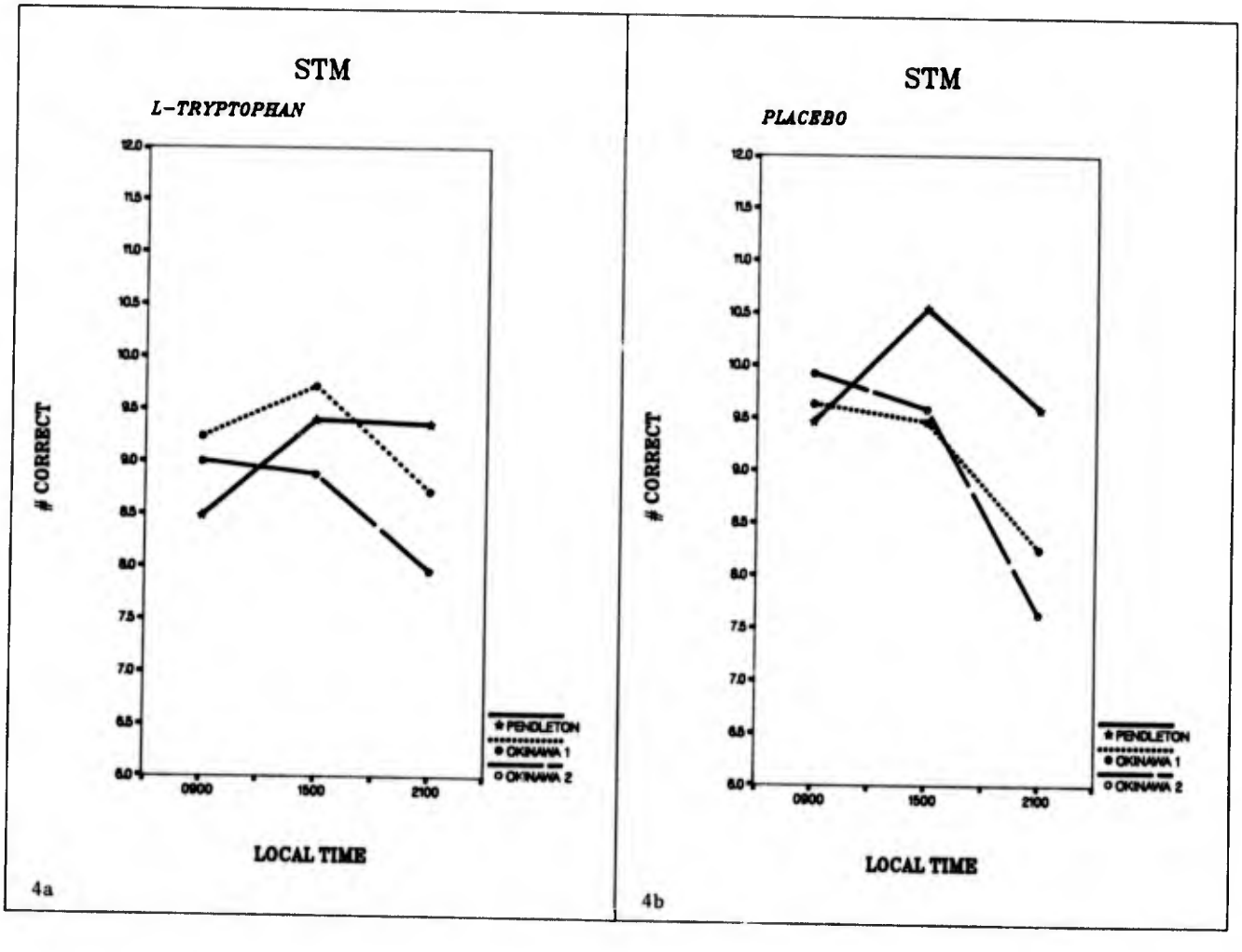


Figure 3. Mean number correct on the Williams Word Memory Test (STM) for the l-tryptophan and placebo groups separately for all test sessions.



Figures 4a & b. Mean number correct on the Williams Word Memory Test (STM) at 0900, 1500, and 2100 on study days B3, O1, and O2 for l-tryptophan and placebo groups, separately.

In order to quantify the degree of performance loss occurring in the evenings according to LT, the numerical change in mean performance at the time of arrival and on each of the two subsequent evenings was compared to the mean performance obtained during battery 7. Results are presented in Table 2a for the DSST, AT, and STM. The calculations were based on all subjects, collapsed over treatment groups. The target shooting percentage decrement was 33%. For RT, in which treatment-group differences were present, the comparable percentages for the placebo subjects were 61.3%, 48.4%, and 19.9%. For l-tryptophan subjects, the percentage decrements were 72.6%, 12.2%, and 7.7%.

Table 2a.

PERFORMANCE LOSS (PERCENT DECREMENT)

Task	Upon Arrival[1]	After 1 Day[2]	After 2 Days[3]
DSST	2.1%	4.4%	-8.4%[4]
AT (attempted)	23.1%	13.9%	3.2%
AT (# correct)	26.0%	14.5%	3.2%
STM	6.3%	10.5%	17.9%

[1]
[2] Battery 16 compared to battery 7.
[3] Battery 19 compared to battery 7.
[4] Battery 22 compared to battery 7.
The negative value indicates that the mean performance score in Okinawa was higher than that of the baseline mean at 2100 on B3.

For comparison, percentage decrement values were also computed using battery 8 data as baseline providing a BT approach by comparing 0300 LT on B3 with the evening test batteries in Okinawa. These results are presented in Table 2b. On RT, for placebo subjects, the percent decrements were 27.4 and 17.3 for the first two nights in Okinawa. RT had recovered by the third night. For l-tryptophan subjects, a 39% decrement was present upon arrival, but RT performance had recovered after the first night of sleep.

Table 2b.

PERFORMANCE LOSS (PERCENT DECREMENT)

Task	Upon Arrival[1]	After 1 Day[2]	After 2 Days[3]
DSST	1.2%	3.6%	-9.4%[4]
AT (attempted)	7.1%	-4.1%[4]	-17.0%[4]
AT (# correct)	8.8%	-6.1%[4]	-20.1%[4]
STM	7.3%	11.5%	18.8%

[1]
[2] Battery 16 compared to battery 8.
[3] Battery 19 compared to battery 8.
[4] Battery 22 compared to battery 8.
The negative values indicate that the mean performance score in Okinawa was higher than that of the baseline mean at 0300 on B3.

Subjective Mood Measures

Because of the large number of subjective variables, an overall review of mood effects will be presented here. As illustrated, mean reported sleepiness on the SSS for the 23 batteries is presented in Figure 5. Mean reported "effort" (that is, "how much of an effort is it to do anything?") for the 23 performance batteries is presented in Figure 6.

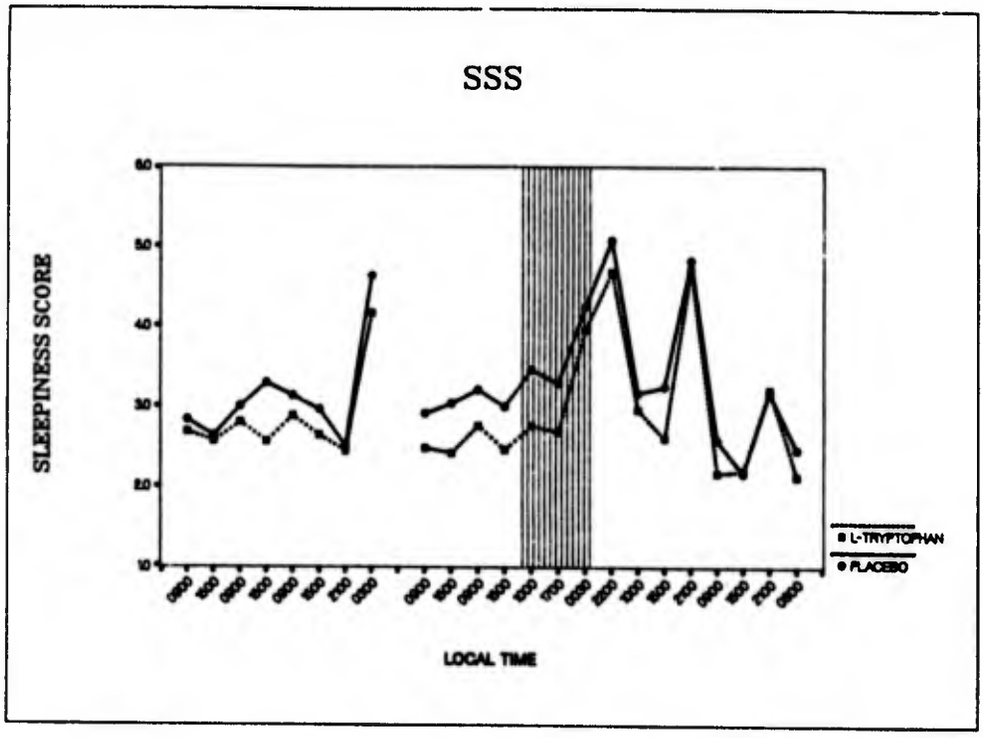


Figure 5. Mean subjective sleepiness on the Stanford Sleepiness Scale (SSS) for the l-tryptophan and placebo groups separately for all test sessions.

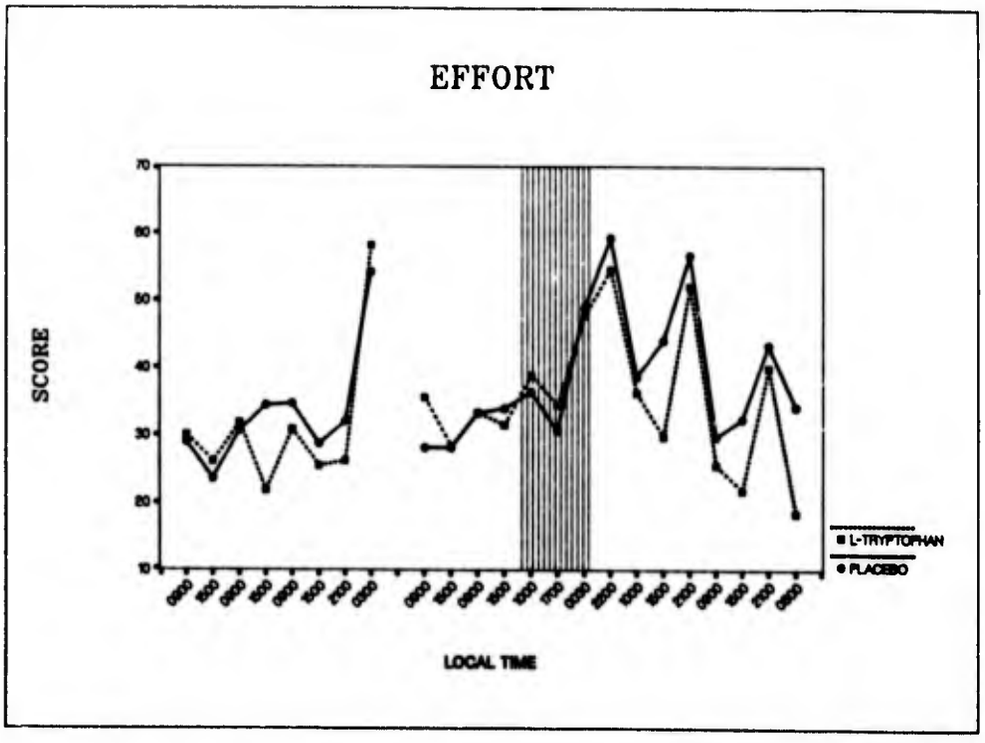


Figure 6. Mean reported "effort" on the Analogue Mood Scales (AMS) for the l-tryptophan and placebo groups separately for all test sessions.

Compared to the same time of day on B3 at Camp Pendleton, all mood measures were significantly worse in the evening at 2100 on O1. Certain measures indicated poorer mood throughout the day on O1: these included more sadness, less happiness, more depression and less vigor. By O2, subjective mood recovered. Overall, mood measures were still worse in the evening on O2, but there were fewer statistically significant comparisons with baseline.

DISCUSSION

L-tryptophan Field Trial

Major goals of this study of transmeridian flight were to document performance and mood changes and to examine the efficacy of two sleep-enhancing interventions in alleviating acute effects of jet lag.

The environmental controls were very effective in increasing the sleep en route, as objectively measured on Medilog subjects in this operational trial, compared to the pilot subjects studied earlier. The elements of those controls were varied and included timing of activities to maximize uninterrupted sleep periods, control of diet, and administration of a "pill". These manipulations alone increased mean sleep time more than 2 3/4 hours compared to mean sleep time of pilot subjects. The l-tryptophan effect aboard the aircraft was not statistically significant, even though the mean increase above placebo was 33 minutes. In laboratory studies of overnight sleep, a mean increase in total sleep time of over 1/2 hour compared to placebo would ordinarily be statistically significant and considered to be substantial. The 52-minute increase in total sleep on the first night in Okinawa was considerable, as well. In this case, the difference between l-tryptophan and placebo groups reached statistical significance. There was no sleep-enhancing effect, though, on subsequent nights. It is important to note that most previous studies reporting positive findings on l-tryptophan emphasized effects on sleep latency rather than total sleep time. In fact, in previous studies, when sleep latency was reported to be reduced, total sleep time was often not statistically increased. In this study in the field, it was impossible to obtain reliable and valid sleep latency measures for individuals and, therefore, we used total sleep time as a measure of sleep-enhancing efficacy. In view of the use of total sleep time rather than sleep-onset time as the dependent measure of efficacy, we were impressed with both the en route and first-night effects.

It may be the case that the absence of sleep-enhancing effects on the second two nights in Okinawa was due to inadequate dose size. On the day of the flight, subjects received two doses of 2 g each, one en route and one after the evening test battery. Our previous sleep laboratory study demonstrating daytime sleep-enhancing effects used a 4-g dose (7).

Upon arrival, significant between-groups differences were present only on subjective measures; l-tryptophan subjects reported more alertness and more positive overall mood. But, on O1, after having obtained significantly more nocturnal sleep time (that is, 52 minutes additional nighttime sleep), the l-tryptophan group differed clearly from the placebo group on one important measure, the faster mean reaction time performance at 2100 on the RT. Probably because it is a longer duration test, RT is very sensitive to sleep-loss effects. The difference between groups on RT showed up at the time of maximal performance loss on several tests, so we are confidant that this RT difference reflects real treatment differences. There is also an indication that STM performance is spared from "jet-lag" effects in the l-tryptophan group on O1. In addition, these data indicate that RT may recover more quickly in l-tryptophan subjects.

There have been no laboratory studies of sleeping pills and next-day performance which demonstrated enhanced next-day performance in subjects who take the active pill compared with those taking the placebo. (For an extensive review of such studies and a comprehensive discussion of sleeping pills and performance effects, see (20)). This study is the first demonstration that improving sleep by psychopharmacological means is associated with enhanced performance on any measure of performance the following day. Perhaps of equal importance, in contrast to sedative-hypnotics, l-tryptophan produced no decrement in performance at any time compared to placebo.

Operational Implications

The field trial results have important implications for westward rapid deployments having operational demands similar to those occurring in this troop airlift. First, the importance of sleep enhancement cannot be overemphasized. By controlling the aircraft environment and administering l-tryptophan 2 g, the company commander can increase total sleep time en route by over 3 hours. L-tryptophan is also effective in enhancing nocturnal sleep after arrival. It is suggested that the appropriate dose for use on the second and third nights after arrival is 4 g.

Second, "jet-lag effects" on performance are problems primarily in the evening and adjustment occurs quickly, for many measures, by the second full day after arrival. Reaction time performance seems to be most sensitive to jet-lag effects and, conversely, to sleep enhancement. If possible, company commanders should avoid nighttime operations on the day of transit and the following day. By the evening of the second full day at destination, the ability to perform calculation quickly and accurately (AT) and decoding performance (DSST) are essentially recovered. Memory performance, though, may continue

to deteriorate over the first 3 nights at destination. The protocol did not extend long enough to identify the time at which short-term memory recovers. Additional justifications for the use of l-tryptophan in the field are that its administration appeared to spare memory to some degree and to hasten readjustment of reaction time performance.

Third, mood upon arrival is generally no worse than would be expected in the middle of the night after a small amount of sleep loss. Throughout the first full day after arrival, mood is poorer than predeployment. If possible, operations requiring positive mood and feelings of alertness and vigor should be scheduled on the second day after arrival.

Extrapolating from both the performance and mood data collected in this study, it appears that military operations would be most effectively conducted in the morning of what would be day 02, the day occurring after 2 nights of sleep and 1 full day at destination. This time frame is consistent with certain U. S. Marine wartime scenarios. Earlier operations would require compensation for performance impairment in the evenings and impaired mood throughout the first day at destination. The above conclusions would probably hold for similar deployments crossing time zones in the westward direction. Results from other published studies suggest impairment following a similar eastward deployment would be greater and persist longer.

Indications for Use of Sedating and Nonsedating Sleeping Aids

As is now known, the RAF aircrews used a sedating sleeping aid, temazepam (Restoril®), in the Falkland conflict in 1982 (21). We have not tested temazepam in our own laboratory because the U. S. formulation of the drug currently available is slowly absorbed and has a much longer half-life than the form of temazepam available in Great Britain. In addition, there is a question about the sleep-inducing efficacy of the U. S. version of temazepam (22, 23). For the RAF, the critical factors permitting use of a sedating sleeping aid were that rest periods occurred on Ascension Island, away from the scene of conflict, and crews were not scheduled to fly again for at least 6-8 hours (21). For similar U. S. operations, triazolam would be a suitable agent for use, based on our laboratory studies.

In the major troop movement by airlift described in this paper, there was a continuing requirement that personnel retain the ability to awaken readily with intact memory and other cognitive and visuomotor skills, both en route and after arrival. When the decision is made that an impairment window is not acceptable, then psychopharmacological support for the mission must involve use of nonsedating sleeping aids.

The decision regarding which pill to employ rests primarily upon consideration of the impairment window (see Table 3). If the environment is safe and the duration of the rest period can be established in advance, then the sedating agent may be the better choice since it acts more rapidly and, perhaps, more consistently than l-tryptophan. (For a discussion, see (7)). However, in other operational environments--aboard aircrafts or in dangerous environments--or for use in brief rest periods of undetermined duration, l-tryptophan would be the agent of choice since its sleep-promoting effects are completely reversible and its use is not associated with an impairment window.

Table 3.

Sleeping Aids for Operational Use

	Sedating	Nonsedating
Agent	triazolam	tryptophan
Class	benzodiazepine	amino acid
Dose	.125-.5 mg	1-4 g
Impairment Window	4-5 h	none
Onset of Action	15 min	45-60 min

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ACKNOWLEDGMENT

This research was supported by the Naval Medical Research and Development Command, Department of the Navy, under research Work Units MR04101.003-0161 and MF58528.002-0001. The views presented in this paper are those of the author and do not reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U. S. Government.

Discussion

Banderet, US

Dr. Spinweber, in the analysis of the rifle shooting, did you also take a look at the amount of time it took the people to actually get those shots out?

Spinweber, US

No, we didn't. Should we have?

Banderet, US

In the future that's one of the things I would be interested in because I've seen this on other operational tasks and from some of our own work. What we find is very seldom does one see a change in accuracy. What changes in the performance is the amount of time it takes people to maintain the level of accuracy that they are accustomed to. And I suppose that was probably operating with your subjects.

Spinweber, US

Well, you know it was such a struggle to get these data, getting the ammunition to Okinawa. You know what operational trials are like. We thought that by using stationary targets which is relatively easy, we wouldn't get any effects at all. And that's why we were so surprised by this 33% decrement.

Moore-Ede, US

First of all, I'd like to congratulate you on the study. I think that it is a tremendous additon to the literature in terms of the control and careful way it was done. And, I must say that I was impressed by treatments that produced no more than 1/2 an hour, for example, of sleep in the aircraft in 54 minutes of extra sleep. That actually adds up quite significantly in terms of performance and in terms of sleepiness on the job. As our studies now in 20 industrial plants that we've combined the data of recently has shown. We've showed that the difference between a group of workers in an industrial situation getting 6 hours of sleep in a 24 hour period while working the night shift versus getting an average 6 1/2 makes an enormous difference. It doubles the number of people who fall asleep on the job or who find themselves nodding off to sleep on the job with 1/2 hour less of sleep. So, rather small changes in the total amount of sleep can have quite a significant effect on performance. So I don't think we should dismiss at all the importance of modifying the amount of sleep by that amount. That is quite a significant amount in terms of performance effects.

Spinweber, US

Thank you for your nice comments, Dr. Moore-Ede. We have also found in the clinical evaluation of hypersomniac patients, we find they don't have sleep apnea and they don't have narcolepsy and they don't have any of the physiological reasons for daytime somnolence. Sometimes its merely just not enough nighttime sleep, and if we put people on a sleep regimen where they sleep for just 1/2 hour more, it makes a huge difference in their daytime alertness.

Terrian, US

You reported that in the laboratory the effect of tryptophan was to decrease the rate of onset of sleep, both during daytime and nighttime. Was the 54 minutes that you gained in the operationasl study consistent with that? That is, was the additional 54 minutes of sleep due to a more rapid onset of sleep or simply an increased duration of sleep?

Spinweber, US

I'm glad you asked that question. That was one of the technical problems that you have in the field. You know, in the sleep laboratory, to measure sleep latency very objectively, you turn out the lights and measure the time till you see the first stage 2 onset. These 51 young men, after they took the tryptophan were told to go back to their barracks and go to sleep. But we had no accurate way of knowing when they really went to bed intending to go to sleep. All other studies of l-tryptophan in the laboratory look at sleep latency, and the effect is a reduction in sleep latency. We were not able to lok at sleep latency in any kind of realistic way so we needed to look at the total sleeptime. My experience though with various studies in the lab is that the reductions of sleep latency compared to placebo, are relatively small, in the range of 50%. So you are talking, at least 1/2 to 3/4 of this being not a sleep latency effect, but a total sleep time effect

FB-111A AIRCREW USE OF TEMAZEPAM DURING SURGE OPERATIONS

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SUMMARY

The objectives of this field study were to evaluate the performance capabilities and sleep patterns of USAF FB-111A aircrews using temazepam as a sleep aid during premission crewrest. Seven 2-man aircrews participated in two data collection periods. During each period, a crew flew a pair of extended duration nighttime missions, one each on consecutive nights. The mission on the first night was an actual FB-111A training mission. The mission the subsequent night was flown in a high-fidelity simulator. Crews were administered 30 mg temazepam for the daytime crewrest interval between one pair of actual and simulated missions and placebo for the crewrest between the other pair of missions. Sleep during daytime crewrest was of longer duration and better quality with temazepam than with placebo. Twelve hours after drug ingestion, aircrew performance of the simulator missions and selected laboratory tests was similar to that with placebo.

INTRODUCTION

FB-111A missions up to 12 hours duration are flown routinely. These long missions in a cramped cockpit typically include a pre-strike aerial refueling, a low-level route, and a post-strike refueling. To meet operational and training requirements, these missions are often conducted at night with takeoff occurring in the afternoon or evening hours. During readiness inspections and other surge exercises, these stressful missions may be imposed upon aircrew already experiencing some cumulative fatigue because of their participation in other surge activities or flying previous missions. The surge-related disruption of aircrew wake/sleep schedules is primarily responsible for this buildup of fatigue, which can reach operationally significant levels. In the case of FB-111A operations, crewmen have reported falling asleep involuntarily for brief periods while airborne, including low-level, terrain-following portions of a mission. An inability to acquire adequate premission crewrest is often reported by these crewmen as a major contributor to their fatigued state.

FB-111A mission effectiveness and safety may be improved for some missions through the medically controlled use of a sleep-inducing drug. Temazepam, a benzodiazepine compound, has been selected by the USAF Surgeon General as a candidate drug for assisting aircrews in acquiring premission sleep under selected operational situations. Temazepam is marketed as offering most of the properties of a desirable short-acting hypnotic, including rapid but not precipitous sleep onset and lack of residual effects on waking (1). Temazepam was used successfully to aid aircrew sleep by the RAF during the Falkland Campaign (2, 3). The objective of this field study was to evaluate the performance capabilities and sleep patterns of FB-111A aircrews using temazepam during premission crewrest.

METHOD

Subjects. The study was conducted at Plattsburgh AFB NY. Seven volunteer FB-111A aircrews, each comprised of one pilot and one navigator, were medically screened prior to participation in the study for any idiosyncratic or allergic reactions to temazepam (Restoril/30 mg). Voluntary informed consent was obtained for each of the crewmen in accordance with AFR 169-3. Thirteen of the 14 crewmen completed all phases of the study. The partial data collected from the pilot of one crew were excluded from analyses when he was unable to complete the protocol due to medical problems unrelated to the study. The navigator assigned to this crew completed his missions with another pilot who did not participate in the study. The mean age of the 13 crewmen was 34.4 years and ranged from 27-43. All rated their health as excellent or good. Mean FB-111A flying time for the crewmen was 825 hours (range: 145-2060 hours). Mean overall flying time was 2419 hours (range: 900-4800 hours).

Design. Each FB-111A crew participated individually in two data collection periods. To allow for other aircrew duties, 2-4 weeks usually elapsed between the two periods. During each data collection period, a crew flew a pair of nighttime missions, one each on two consecutive nights. The mission scheduled on the first night (the FB-111A mission) was an actual long-range training mission originating and terminating at Plattsburgh AFB. The mission on the subsequent night (the simulator mission) was scheduled to be "flown" from 2100-0300L in the FB-111A simulator at Plattsburgh AFB. The FB-111A missions were scheduled to begin in the afternoon and end around midnight. Regardless of the time of FB-111A mission completion, the crewmen were required to remain awake at the squadron facility until about 0600L. At 0600L they were issued a capsule to be taken at their residences at 0700L, 12 hours prior to the 1900L reporting time for the simulator mission to be flown later the same day. A crew was administered temazepam/30 mg for the daytime crewrest between one pair of missions and an identically appearing placebo for the crewrest between the other pair of missions. Four crews received temazepam during their

first data collection period and three received placebo during their first data collection period. Neither the participating crewmen nor the data collectors/evaluators were aware of the treatment schedule.

Self-Report Subjective Measures. Upon reporting for both the FB-111A missions and the simulator missions the crewmen completed a sleep survey, a mood survey, a subjective symptoms survey, and a subjective fatigue rating scale. The sleep survey recorded the recent sleep history. The Profile of Mood States (POMS) provided standardized T-scores on the affective dimensions of tension, depression, anger, vigor, fatigue, and confusion. The subjective symptoms survey presented 20 physiological symptoms which were rated from 0-7 in severity (Fig. 1). Selfratings of fatigue were collected using the 7-point scale on the Crew Status Survey (Fig. 2). The crewmen were instructed to always respond "as to how they felt right now" when completing the mood, symptom, and fatigue surveys. A questionnaire addressing the quality of sleep acquired during daytime crewrest was also completed by the crewmen when they reported for the simulator mission. The 7-point Stanford Sleepiness Survey (*1-alert, wide awake; 7-almost asleep*) was included in this questionnaire. After each FB-111A and simulator mission the crewmen again completed a symptom survey and a fatigue rating. While the self-report data collected before and after the FB-111A missions were of some interest, the primary function of these administrations was to acquaint (or, in the case of the second data collection period, reacquaint) the crewmen with the survey procedures in preparation for data collection immediately before and after the simulator mission.

Activity Monitoring. Each crewman's activity was recorded continuously during each data collection period using Walter Reed Activity Monitors (4). These monitors are small (1.6x2.5x.6 inches), lightweight (3 oz), sealed units containing a miniature battery-driven computer with solid state memory and triaxial accelerometers. Activity data are collected by wearing the monitor on the wrist like a watch. Subtle arm and wrist movements are sensed by the monitor's electronics and stored as a function of time in resident memory for later retrieval. The activity monitor was developed by the Walter Reed Army Institute of Research as a means of objectively recording periods of activity and inactivity from a large number of soldiers participating in sustained field exercises. In this study, wrist movements were counted for each 2-minute epoch. These data were evaluated for differences in daytime sleep duration and quality with and without the presence of temazepam. Data from the 12-hour (0600-1800L) segment involving the daytime crewrest interval within each data collection period were individually scored for active and inactive states. The active state was defined as awake and the inactive state as asleep. Awakenings were defined as any cluster of activity three or more epochs long (i.e., 6 minutes or more) in which continuous scores were greater than 25 movements/epoch and which occurred in a field of data predominantly scored as sleep. From these scores, total sleep time and number and duration of sleep awakenings were derived for each crewrest interval.

Performance Testing. During the hours between completing the first FB-111A mission and departing for home at 0600L to begin crewrest, the crewmen were trained and practiced on three laboratory performance tasks: the code substitution task, the Wilkinson four-choice reaction time task, and the Williams word-memory test. The crewmen were refamiliarized with the tasks following the FB-111A mission of their second data collection period. The performance tasks were administered for testing purposes before and after each simulator mission. Each crewman was tested individually in a closed room. The tasks were selected because they require little training time and they have been shown to be sensitive to the effects of temazepam and other benzodiazepines (5, 6, 7, 8). The code substitution and the reaction time tasks were modified versions of the Automated Portable Test System developed by Essex Corp. and automated on a NEC (model 8201A) microcomputer.

Code Substitution Task. This task is a modification of the digit symbol substitution test (9). On each trial nine different letters are randomly paired with the numbers 1-9 in the upper half of the LED screen of a NEC computer. These pairings are continuously displayed for reference during each 90-second trial. In the lower half of the screen, single letters from the nine are randomly highlighted one at a time. The subject's task is to identify the number paired or "coded" with the highlighted letter and enter it in the keyboard. As soon as an entry is made, another letter is highlighted. Subjects are instructed to decode as many letters as possible in 90 seconds. The number of attempts, number correct, percent correct, and average response time are scored.

Wilkinson Four-Choice Reaction Time Task. This task is a self-paced, choice reaction time test. The rectangular cursor of the NEC computer serves as a visual stimulus which randomly appears at one of four locations on the LED screen. The four stimulus locations are fixed in a row at the bottom of the screen. Each location is associated with one of four function keys located in the top row of the keyboard directly below the screen. The four function keys correspond in position to the four stimulus locations. The subject's task is to press the corresponding function key when the cursor occurs at one of the four locations. As soon as a response occurs, correct or incorrect, the cursor disappears and immediately reappears in random fashion at any one of the four locations. Task duration for this study was 6 minutes. Subjects are instructed to respond as quickly as possible without making errors. The number of attempts, number correct, percent correct, average reaction time, and number of responses longer than 1.0 second (blocks) are scored.

Williams Word Memory Test. This task evaluates short-term memory (10). The subject is presented a tape-recorded list of 15 words. The female voice on the tape pronounces each word, spells the word, and then repeats the word again. The subject writes down each word as it is presented. After hearing all 15 words, the subject is allowed 3 minutes to

write down in any order as many of the words as he can recall. The subject is then given a typed list of 30 words within which the 15 words from the list are randomly presented. The subject is instructed to circle as many of the 15 words from the list as he can recognize. Words are never repeated between lists. A different list was presented at each training and testing session. All subjects received the same lists in the same order.

Simulator Mission Evaluation. The performance of each crew during the simulator missions was evaluated by one of two teams of instructor-rated FB-111A crewmen. The two evaluator teams were each comprised of a pilot and a navigator. An aircrew was evaluated by the same team during both of their simulator missions. For the purposes of this study, the performance of each crewman during each of 9 mission segments was rated by his evaluator-counterpart on an 11-point scale. The anchor points for the scale were: *1-worst I have ever seen; 6-average; and 11-best I have ever seen.*

Statistical Analyses. Comparisons between crewrest with temazepam and placebo were made on the data collected immediately before and after the simulator mission. Performance scores, mood scores, activity data, and total hours slept were analyzed by paired t-tests. Aircrew subjective self-reports and evaluator ratings of simulator performance were analyzed with the Wilcoxon matched-pairs signed-ranks test. All tests were two-tailed.

RESULTS

Mission Summary. The FB-111A missions ranged from 2.0-8.5 hours in duration. Some FB-111A missions were of shorter duration than planned as a result of late departures or poor weather at the desired target range. Four FB-111A missions, all by chance preceding crewrest with temazepam, were cancelled due to weather or maintenance problems. Aircrew whose FB-111A missions were shortened or cancelled spent the remainder of the night awake at the squadron facility and participated in all other aspects of the study just as if they had flown. All simulator missions were completed as scheduled, although one aircrew was not monitored by the same evaluation team on both of their simulator missions.

Daytime Sleep. Upon reporting for the simulator mission at 1900L, the crewmen completed the self-report questionnaires on the quantity and quality of sleep acquired during the daytime crewrest interval. The crewmen consistently reported being tired and ready to go to sleep at 0700L. The mean sleep latencies as determined by self report were 7.7 minutes with temazepam and 11.3 minutes with placebo. Ten of the 13 crewmen reported sleeping longer with temazepam, 1 slept less, and 2 reported no difference. The mean total hours reported slept were 7.5 hours with temazepam and 6.3 hours with placebo ($p<.01$). Although not significant, mid-sleep awakenings were reported more frequently for the placebo condition than the temazepam condition ($p<.10$). Nine of the crewmen reported at least one mid-sleep awakening with placebo whereas only 4 crewmen reported awakenings with temazepam. After sleeping with temazepam, the crewmen felt more rested ($p<.05$) and reported the daytime sleep to be more similar to their typical nighttime sleep ($p<.05$). Capsule effectiveness was rated higher after sleeping with temazepam than with placebo ($p<.05$). The mean rating on the 7-point Stanford Sleepiness Scale was 2.3 following daytime sleep with temazepam and 3.0 with placebo. The difference was not statistically significant ($p<.10$).

Activity During Sleep. Activity data were successfully collected during both daytime crewrest intervals for 10 crewmen. The raw data for each of these crewmen when sleeping with temazepam and placebo are presented in Figure 3. A general pattern of greater sleep disruption and reduced sleep duration is discernible for the placebo condition. The analysis of the activity scores revealed 9 of the 10 crewmen to have slept longer during crewrest with temazepam than placebo. Mean total time slept was 7.7 hours for temazepam and 6.6 hours for placebo ($p<.005$). As determined by this analysis, the number of crewmen reporting mid-sleep awakenings was similar for the two drug conditions. Seven of the crewmen reported awakenings with temazepam; eight reported awakenings with placebo. The analysis also indicated a notable, but statistically nonsignificant, difference in the mean total duration of mid-sleep awakenings - 10 minutes for temazepam and 53 minutes for placebo ($p<.10$).

Mood. The mean POMS T-scores collected from the crewmen as they reported for the simulator missions are presented in Table 1. There were no effects related to crewrest with and without temazepam for any of the six affective dimensions.

TABLE 1

MEAN T-SCORES ON POMS AFTER DAYTIME CREWREST

	Temazepam	Placebo
Tension	36.2	37.8
Depression	37.7	38.5
Anger	39.5	39.4
Vigor	52.0	46.7
Fatigue	39.4	42.9
Confusion	34.6	36.5

Subjective Fatigue. There were no significant effects for fatigue ratings related to crewrest with temazepam and placebo. However, significant changes in subjective fatigue occurred from start to finish of both the FB-111A missions and the simulator missions ($p<.01$ in all cases). The overall distributions of the frequencies of fatigue responses to the Crew Status Survey for the FB-111A and simulator missions are presented in Table 2. A mean fatigue rating of 2.0 was reported prior to the FB-111A missions. After the missions, fatigue increased to a mean response of 4.2. Following 12 hours of crewrest, fatigue recovered to a mean rating of 3.0 when reporting for the simulator mission. On completion of the simulator mission the mean fatigue rating was 4.5. The findings for the ratings of fatigue on the symptoms survey coincided with those of the Crew Status Survey. Of the 20 symptoms listed on the symptoms survey, only "Fatigue" was reported frequently enough to bear meaningful evaluation.

TABLE 2

FATIGUE RATING FREQUENCIES ON CREW STATUS SURVEY

		FB-111A Mission		Simulator Mission	
		Pre	Post	Pre	Post
1	Fully Alert; Wide Awake; Extremely Peppy	5		4	1
2	Very Lively; Responsive, But Not at Peak	16		3	1
3	Okay; Somewhat Fresh	4	6	11	2
4	A Little Tired; Less Than Fresh	1	8	4	4
5	Moderately Tired; Let Down		12	4	15
6	Extremely Tired; Very Difficult to Concentrate				3
7	Completely Exhausted; Unable to Function Effectively; Ready to Drop				

Performance Testing. After completing the questionnaires, the crewmen were tested on the three performance tasks. Aircrew performance 12 hours after capsule ingestion was consistently similar for the temazepam and placebo conditions (Table 3). While four-choice reaction-time response accuracy was very high under both the temazepam and placebo conditions (98.5% and 99.2%, respectively), these data provided the only statistically significant ($p<.025$) drug-related effect for any of the laboratory performance measures. Memory recall was better after sleeping with placebo than temazepam, but this difference was not statistically significant ($p<.10$). There were no drug-related differences in the performance data collected after the simulator mission, approximately 20 hours after capsule ingestion.

Simulator Mission Performance Ratings. Drawing on two pilot-navigator evaluation teams, eleven crewmen had their performance on both of their simulator missions rated by the same evaluator. Mean ratings for each of 9 mission segments following daytime crewrest with temazepam and placebo are presented in Table 4. There were no significant drug effects for any of the 9 mission segments. Overall simulator rating scores were derived for each crewman by calculating the mean rating for the 9 segments that comprised a mission (Table 5). Analysis of these scores indicated simulator performance following crewrest with placebo was significantly better than that with temazepam ($p<.05$), although the difference was small.

DISCUSSION

The objectives of this field study were to evaluate the effects of a single 30 mg dose of temazepam on (a) performance 12 hours after ingestion, and (b) the quantity and quality of daytime sleep. The findings replicate those of previous laboratory studies and extend the information available on the use of temazepam in real-world operations involving disrupted wake/sleep schedules. Compared to placebo, overnight doses of 20 and 30 mg temazepam generally have been reported to reduce sleep onset latency, reduce the number and duration of awakenings, increase total sleep time, and improve the subjective quality of sleep (11-13). Afternoon sleep with 10 and 20 mg temazepam has been reported by healthy subjects to be of better quality than that with placebo, although analysis of sleep EEGs indicated no differences for total sleep time and sleep onset latency (14). In our study, both the aircrew subjective reports and the sleep-activity data indicated improved daytime sleep to have occurred with temazepam. We found no difference due to drug for subjective estimates of sleep onset, as the crewmen reported falling asleep in about 10 minutes with and without temazepam. The requirement for the crewmen to remain awake throughout the previous night very likely generated adequate fatigue and sleepiness to make falling asleep at 0700L not a problem. Thus, under the conditions of this study, the 30 mg dose of temazepam primarily exerted a benefit by enhancing sleep duration and continuity.

TABLE 3

MEAN COGNITIVE PERFORMANCE AFTER DAYTIME SLEEP

	Temazepam $\bar{X}$ (SD)	Placebo $\bar{X}$ (SD)	Difference $\bar{X}$ (SD)
Code Substitution			
Reaction time (ms)	1972.4 (299.5)	1930.1 (217.3)	42.3 (245.6)
Standard deviation (ms)	568.8 (165.9)	507.1 (111.8)	61.7 (174.5)
Number correct	40.2 (6.1)	41.5 (4.9)	-1.3 (6.0)
Number attempted	41.3 (5.8)	41.9 (4.4)	-0.6 (4.6)
Percent correct	97.2 (4.0)	98.8 (2.4)	-1.7 (4.8)
Four Choice Reaction Time			
Reaction time (ms)	462.5 (52.8)	463.1 (37.7)	-0.5 (36.9)
Standard deviation (ms)	76.8 (14.3)	73.2 (16.5)	3.7 (13.6)
Number correct	577.7 (42.1)	578.7 (32.8)	-1.0 (30.5)
Number attempted	586.7 (48.0)	584.5 (35.9)	2.2 (34.7)
* Percent correct	98.5 (1.6)	99.2 (1.0)	-0.6 (0.9)
Short-Term Memory			
Number recalled	8.4 (2.3)	9.6 (2.4)	-1.2 (2.4)
Number recognized	13.2 (1.9)	13.5 (1.5)	-0.2 (2.0)

* $p < .05$

TABLE 4

SIMULATOR MISSIONS: MEAN PERFORMANCE RATINGS BY SEGMENT
(1: worst ever seen; 6: average; 11: best ever seen)

Mission Segment	Temazepam	Placebo
Takeoff	7.8	8.2
Cruise	7.4	7.5
Aerial Refueling-1	7.6	7.6
Aerial Refueling-2	7.4	7.7
Low Level	6.9	7.5
Bombing	7.5	7.7
Missile Firing	7.3	7.9
Landing	7.3	7.9
Emergencies	8.4	8.0

TABLE 5

SIMULATOR MISSIONS: MEAN PERFORMANCE RATINGS BY CREWMAN

Crewman (Rater)	Temazepam	Placebo
Navigator 1 (B)	8.0	8.4
Pilot 2 (C)	8.4	8.9
Navigator 2 (D)	6.7	7.5
Pilot 3 (C)	6.6	6.3
Navigator 3 (D)	7.2	7.2
Pilot 5 (A)	7.8	8.0
Navigator 5 (B)	5.8	5.7
Pilot 6 (A)	9.0	9.0
Navigator 6 (B)	9.0	9.3
Pilot 7 (C)	6.9	7.6
Navigator 7 (D)	7.2	7.2
* Mean	7.5	7.8

* $p < .05$

While benzodiazepine compounds such as temazepam generally improve the quality of sleep, they have not been found to improve the quality of post-sleep performance. The effects of temazepam on performance have been reviewed by Johnson and Chernik (6) and Heel et al (12). For single doses in the 20-30 mg range, significant impairment of cognitive and psychomotor performance is usually detectable within the first 2 hours post ingestion, occasionally detectable up to 6 hours, and infrequently reported beyond 10 hours (6, 11-13, 15-27). Laboratory tests involving speed of performance are usually the most likely to be impaired by benzodiazepines (6, 27). In this study, several measures of performance, some involving speed, detected no notable differences in crewman skills 12 hours after ingestion of 30 mg temazepam and placebo. Two statistically significant drug-related differences in performance - percent correct responses on the four-choice reaction time task and overall mean ratings of flight simulator performance - were both in favor of better performance with placebo than temazepam. While worthy of documentation, close inspection of the data suggests these findings are not of operational significance. Mean percent correct responses on the four-choice reaction time task were extremely high for both temazepam and placebo conditions--all but 2 of the 26 scores were 98% or higher, 7 of the crewmen scored the same percentage under both conditions, and 5 of the remaining 6 crewmen scored only a 1% difference in favor of the placebo condition. The overall mean ratings of simulator performance following crewrest were better than average for both the temazepam and the placebo conditions, and differed by only 0.3 of a point on the 11-point rating scale. The instructor-qualified evaluators considered this difference to be operationally insignificant.

A potentially important side effect of benzodiazepines is the occurrence of anterograde amnesia; loss of memory for events occurring or material learned after drug administration. The incidence and characteristics of anterograde amnesia produced by benzodiazepine compounds have not been well established. What is currently known comes from both objective studies (6, 8, 28, 29) and anecdotal reports (30). In a nonexhaustive review of the literature, we were able to identify only a few studies which had previously attempted to evaluate the effects of temazepam on short-term memory. Roth et al (25) found short-term memory to be impaired by a 30 mg dose of temazepam 3.5 hours after ingestion, but not at 10.0 and 22.5 hours. Liljequist and Mattila (20) found no memory impairment for 10 and 20 mg doses of temazepam 1, 3, and 8 hours after ingestion. Pleuvry et al (23) anecdotally reported memory deficit for a 40 mg but not a 20 mg dose of temazepam. Using the Williams word memory test, Spinweber and Johnson (8) demonstrated anterograde amnesia for 0.5 mg triazolam at 1.5, 3.0, and 5.0 hours but not at 8.25 hours post ingestion. Because temazepam and triazolam are similar benzodiazepines, we used the same memory test in this study and found no reliable effect on short-term memory recall 12 hours after taking an oral dose of 30 mg temazepam.

Nicholson (2) reported that 20 mg temazepam was useful in helping UK aircrews acquire sleep at irregular times of the day during the Falkland Islands Campaign. Due to critical operational requirements, crewmen sometimes flew missions as soon as 6 hours after ingestion of drug with no untoward effects. This experience is a primary factor in promoting interest by the USAF in using temazepam as a biochemical means of enhancing aircrew performance and safety. However, it is important to bear in mind that temazepam is produced in a soft gelatin capsule in the UK and in a hard gelatin capsule in the US. The different preparations are not absorbed and eliminated at the same rate. Hindmarch (18) reports morning-after hangover effect for temazepam in the hard but not the soft capsule formulation. A soft gelatin capsule is soon to be made available in the US. At that time, the importance of capsule formulation should be evaluated in a simulated operational environment involving repeated doses.

The evidence indicates that single 30 mg oral doses of temazepam may be used effectively as a sleep aid for aircrews conducting tanker, transport, and bomber operations involving irregular duty schedules. Because temazepam is a muscle relaxant, additional evaluation should be conducted on G-tolerance effect prior to aircrew use in high-G tactical operations.

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ACKNOWLEDGEMENTS

Lt Col Daniel P. Redmond, Walter Reed Army Institute of Research, provided the activity monitors and directed analysis of the activity data. Dr Cheryl L. Spinweber, Naval Health Research Center, provided the Williams word-memory tapes and valuable guidance on evaluating the effect of drugs on performance. Mr. Joseph R. Fischer, Jr., USAFSAM Crew Support Branch, directed the statistical analyses at USAFSAM. The placebo capsules were supplied by the Sandoz Company.

NAME:_____ Date: _____

_____ Time: _____

SUBJECTIVE SYMPTOMS QUESTIONNAIRE

INSTRUCTIONS: Indicate whether you are experiencing any of the symptoms below right now by circling NO or YES to each item. If you answer YES, circle the number which best describes the severity of the symptom.

				SLIGHT			MODERATE			SEVERE
1.	Headache.....	NO	YES	1	2	3	4	5	6	7
2.	Light headedness/dizziness...	NO	YES	1	2	3	4	5	6	7
3.	Rapid breathing.....	NO	YES	1	2	3	4	5	6	7
4.	Irregular breathing.....	NO	YES	1	2	3	4	5	6	7
5.	Nausea.....	NO	YES	1	2	3	4	5	6	7
6.	Rapid heartbeat.....	NO	YES	1	2	3	4	5	6	7
7.	Pounding heartbeat.....	NO	YES	1	2	3	4	5	6	7
8.	Weakness.....	NO	YES	1	2	3	4	5	6	7
9.	Sweating.....	NO	YES	1	2	3	4	5	6	7
10.	Visual disturbance.....	NO	YES	1	2	3	4	5	6	7
11.	Muscular incoordination.....	NO	YES	1	2	3	4	5	6	7
12.	Fatigue.....	NO	YES	1	2	3	4	5	6	7
13.	Numbness.....	NO	YES	1	2	3	4	5	6	7
14.	Tingling.....	NO	YES	1	2	3	4	5	6	7
15.	Apprehension.....	NO	YES	1	2	3	4	5	6	7
16.	Hot flashes.....	NO	YES	1	2	3	4	5	6	7
17.	Cold flashes.....	NO	YES	1	2	3	4	5	6	7
18.	Euphoria.....	NO	YES	1	2	3	4	5	6	7
19.	Irritability.....	NO	YES	1	2	3	4	5	6	7
20.	Inability to think clearly...	NO	YES	1	2	3	4	5	6	7
21.	Other symptoms ?									

Figure 1. The Subjective Symptoms Questionnaire was completed before and after each FB-111A and simulator mission.

NAME | DATE AND TIME

SUBJECTIVE FATIGUE

(Circle the number of the statement which describes how you feel RIGHT NOW.)

1	Fully Alert; Wide Awake; Extremely Peppy
2	Very Lively; Responsive, But Not At Peak
3	Okay; Somewhat Fresh
4	A Little Tired; Less Than Fresh
5	Moderately Tired; Let Down
6	Extremely Tired; Very Difficult to Concentrate
7	Completely Exhausted; Unable to Function Effectively; Ready to Drop

COMMENTS

WORKLOAD ESTIMATE

(Circle the number of the statement which best describes the MAXIMUM workload you experienced during the past work period. Put an X over the number of the statement which best describes the AVERAGE workload you experienced during the past work period.)

1	Nothing to do; No System Demands
2	Little to do; Minimum System Demands
3	Active Involvement Required, But Easy to Keep Up
4	Challenging, But Manageable
5	Extremely Busy; Barely Able to Keep Up
6	Too Much to do; Overloaded; Postponing Some Tasks
7	Unmanageable; Potentially Dangerous; Unacceptable

COMMENTS

PREVIOUS EDITION WILL BE USED

SAM FORM 202 APR 81 — CREW STATUS SURVEY

Figure 2. Selfratings of subjective fatigue were collected using the 7-point scale on the upper portion of the Crew Status Survey.

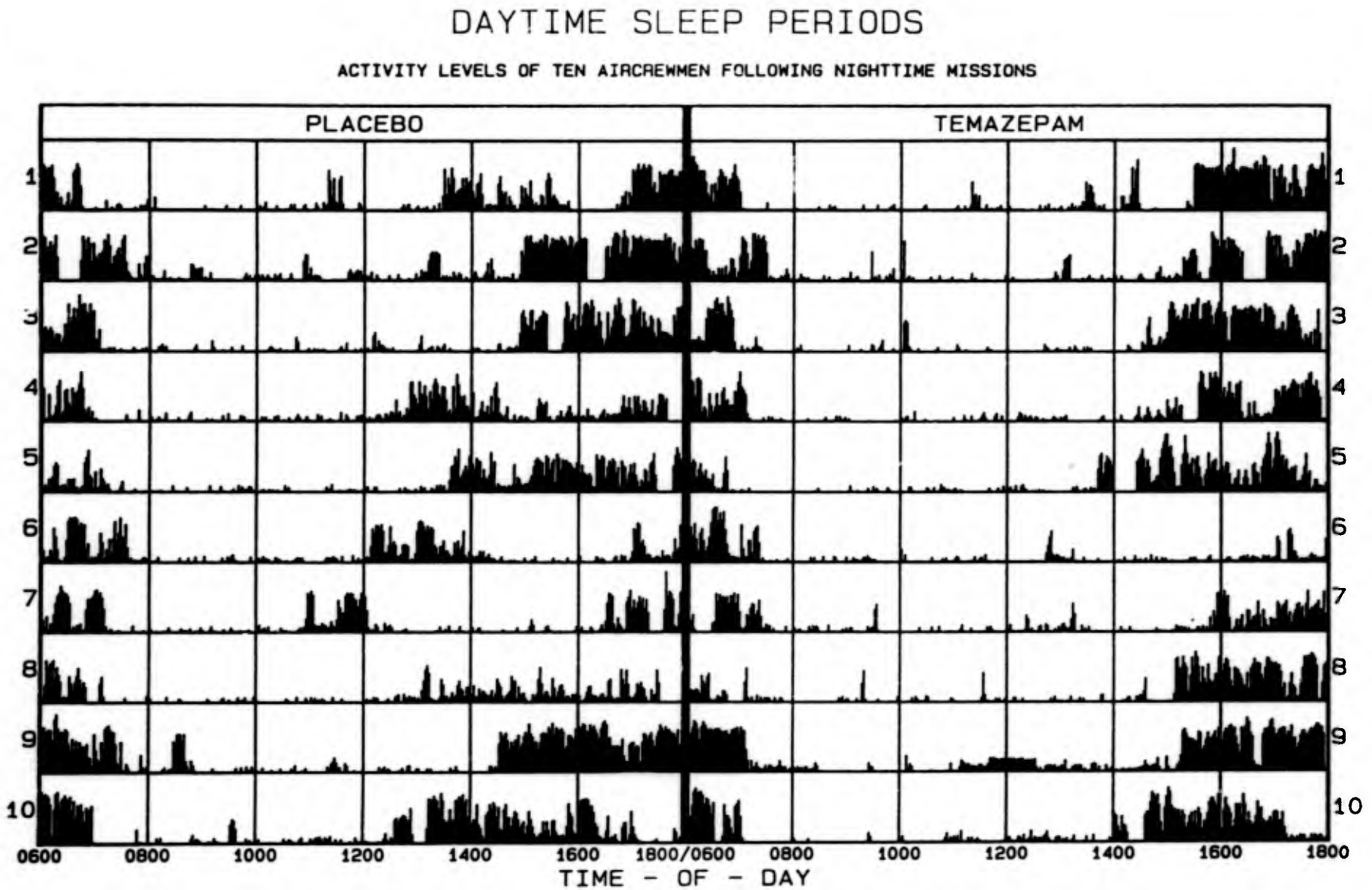

Figure 3. Raw activity data during daytime crewrest and sleep with temazepam and placebo. The ordinate scale for each of the 10 crewmen reflects up to 1,000 counts per 2-minute epoch.

Discussion.

Moore-Ede, US
. . (not recorded). . issues related to the design which I understand was difficult to achieve in an operational setting like the one you were studying. One is, the biggest difference that you see between sleep-deprived and non-sleep-deprived individuals in performance occur in a period of time that appears to be sort of towards the tailend and just after your simulator test. In other words, in the 3AM to 5AM range. And I could imagine that if the evaluaters were scoring for a 6 hour period that started at 9 o'clock in the evening and ended at 3 o'clock in the morning, and grouped that evaluation together you might not see differences that you would see if perhaps you broke down hour by hour and looked at what happened between 2AM and 3AM or, and I understand it wasn't feasible in this case, extended to that key time between 3 and 5AM when big differences can occur in terms of performance. Did you manage to break that data down hour by hour?

Storm, US
Yes, there were nine segments involved with the landing being the last part of the simulator mission, and it was not necessarily the worst case. Also, we did the performance test after that again at that point in time, and your point is well-taken. That would be 3:30 or 4 in the morning. They did just fine.

Spinweber, US
I think it is important to point out that the temazepam you used and that we have available to us in the US is very different pharmacokinetically from the temazepam that the RAF had available to them. The formulation in the US is in a hard gelatin capsule and there's questions about whether it really has any sleep-inducing efficacy and there's also questions about its half life which might be as long as 14 to 15 hours with a range of 8 to 38 hours in the most recent study. I was relieved to see that you didn't find any performance decrements at 12 hours. I think your sleep latency data, if I am correct, there was no difference between placebo and drug, fits in with what we think is true about the American formulation, although your placebo subjects went to sleep very quickly.

Storm, US
They didn't need a drug to go to sleep. Having been up all night, I think the drug here, if it had any effect, was to allow them to stay asleep during the day.

Spinweber, US
I think you collected, though, incredibly important data for us in research too and that is that simulator performance does seem to show a decrement soon after administration of these drugs, and that's always the question that the operational people ask us. I know that on triazolam at about 1 or 2 hours after administration I can tell unfortunately, who got the drug because they have trouble navigating and doing other things as we walk them down the hall. Do you have any sense of how impaired your temazepam people were?

Storm, US
Well, of course, we didn't see them either. They would drive home and then take the capsule in their normal sleeping environment and we did not witness that.

Spinweber, US
But how about later when they came back?

Storm, US
When they would come in some would say "I know I got it. No doubt. I slept like a baby. I got it." We didn't really keep track of that. I had a feeling about 50-50 as to how accurate they were. I did feel like they could be more accurate about it and I think this has been discussed in the literature that you are more familiar with than I. They could be more accurate about it if they happened to get the drug second.

Spinweber, US
What about when they came back for acute testing though in the simulator? Weren't they identifiable as drug subjects?

Storm, US
Oh yeah, not too, not too. It was blind again. It was blind again. We had very few subjects there. What we did there was we told the evaluators, double blind, you know, some will, some won't. We only had six or eight crewmen we did on two nights. We didn't get everybody back. And we didn't give everybody drug because. . .

Spinweber, US
Oh, I see. So you told the evaluators everybody got the drug, but only some of them got the drug.

Storm, US
They all got the drug, but we told the evaluators half did and half didn't, because we had such a small group. . .

Spinweber, US
So, I was going to say they tend to be noticeable, acutely after administration, that they are impaired.

Storm, US
To me there was a terrific time effect during that first hour and 1/2. Some people maybe were showing or acting , a little different at 30 minutes where others didn't. Maybe at an hour and 1/2 they had. The individual differences do concern me a great deal but I'm not good enough at it yet to say what they are.

Spencer GE
I've a question and a comment for Dr. Spinweber, if we can do that already at this point. Concerning the short term memory data, you showed on your word recall task that even in the first phase before the transport there was a slight fall in accuracy. If I recall the graph correctly and then once they were in Okinawa there was a rather drastic fall in accuracy. And I wonder if you've done any subjects without such a transport for such a long period of time on your tasks because as you know such word recall tasks, especially with a rather reduced pool of words, you can get a very large proactive interference effect. That means the previous tests they've had interact and interfere more and more with the next test and the next test. So the question is, did you do this? And the inference is, if you didn't its hard to interpret to what extent the jet lag actually caused legitimate short term memory effects.

Spinweber, US
That' s good question and something you need to be very careful of in these repeated measures of performance. The early decline before the flight I interpret to be actually a sleep loss effect. The Marines take away the pillows and the blankets the day in advance to pack them aboard the plane and so there is this accrual of sleep debt even before they get on the plane. That is so similar to our sleep loss data that I think that's what it is. We also scored all these test sets for intrusion errors and other kinds of errors to try to be sure that wasn't what we were having and my sense is, no that isn't, we weren't having a problem with that effect. But that's a very good point. And, you know, in some of the other data, we had a problem with the opposite effect, a big learning curve that we just couldn't get rid of even with mass trials.

Billings, US
Dr. Storm, with respect to your simulation flight evaluations and evaluators, you indicated to Dr. Moore-Ede's question that there were not necessarily more effects during the last phases of the mission. Did you have any way of controlling at all the level of fatigue that was present in the evaluators who, after all, were doing these evaluations at a ridiculous hour in the morning?

Storm, US
We did pretty well. For most of it those four people got some rest that afternoon before they came on duty, not in every case. We were more concerned about getting the same person than we were about having them rested. But that's a good point. But for the most part there was some afternoon rest.

Billings, US
The reason I ask is because errors of omission are a good deal more common than errors of commission in what effectively is a passive monitoring task that the evaluators were performing.

Storm, US
Yes. All I can say is that I watched then to some extent and I was tired too. But they did very, very well. I will point out to those who are interested that they were instructor-pilots.

LES MANIFESTATIONS PHOBIQUES CHEZ LES PILOTES CONFIRMES

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RESUME

Les manifestations phobiques de peur en vol ne sont pas rares chez les pilotes confirmés. Les expressions cliniques peuvent en être multiples et diverses : psychologiques, somatiques ou comportementales. Une intervention thérapeutique précoce dans les états aigus réactionnels est souvent favorable. Le pronostic est plus incertain dans les états pathologiques organisés et évoluant de façon chronique.

Dés le début de l'aviation, des troubles psychopathologiques ont été décrits chez les pilotes sous le terme d'"aéronévroses". En 1912, dans la préface du premier ouvrage de Médecine Aéronautique, Charles Richet écrivait : "le principal péril est dans la psychologie même de l'aviateur". En dépit des progrès très importants accomplis dans la mise au point des aéronefs et du matériel d'équipement et de protection ainsi que dans la sélection et l'entraînement des pilotes, il n'est pas rare d'observer des manifestations psychopathologiques susceptibles de compromettre l'adaptation professionnelle, la sécurité aérienne et l'efficacité opérationnelle des pilotes.

On regroupe habituellement ces troubles sous le terme de "peur du vol" (fear of flying) ou "phobie du vol".

I - INTRODUCTION

Le terme de peur est généralement réservé à un ensemble de manifestations émotionnelles aiguës éprouvées par un sujet confronté à une situation de danger. Ce danger est un danger réel, précis et situé dans la réalité extérieure. L'émotion éprouvée s'accompagne de manifestations somatiques diverses, motrices, sensorielles et neuro-végétatives. La peur peut avoir une certaine fonction adaptative, quand elle reste limitée et contrôlée, en prévenant l'organisme du danger et en élevant son niveau de vigilance. Quand les manifestations sont particulièrement intenses et répétées et débordent les mécanismes adaptatifs, (on parle alors de "stress"), elles peuvent entraîner des troubles fonctionnels durables, voire des lésions somatiques : hypertension, ulcère, colopathies, etc... L'accoutumance, l'entraînement et le désir profond du sujet d'affronter la situation dangereuse (la motivation) permettent de développer des capacités adaptatives et de faire disparaître les manifestations de peur.

L'angoisse ou l'anxiété correspond à un état proche des manifestations de la peur, mais en dehors d'une situation de danger concret, présent et extérieur. Il s'agit alors d'un sentiment de danger intérieur et en l'absence d'une situation dangereuse, le sujet ne sait pas exactement de quoi il a peur.

Dans la phobie, l'angoisse apparaît face à des situations concrètes et extérieures, mais qui n'ont pas en elles-mêmes un caractère objectivement dangereux. On considère alors que c'est la signification symbolique de cette situation qui est à l'origine du sentiment interne de danger éprouvé par le sujet.

Pour quelqu'un qui n'a jamais volé, on conçoit que le vol puisse représenter une situation dangereuse et l'accident aérien est en effet une réalité bien concrète. Mais nous ne décrirons pas ici les manifestations psychopathologiques diverses et variées qui accompagnent le travail d'adaptation au cours de l'apprentissage aérien. Un apprentissage réussi étayé par une motivation de bonne qualité permet au pilote adapté de ne plus éprouver de manifestations anxieuses sinon qu'occasionnelles en vol. Pour un pilote adapté, le vol a perdu la signification d'une situation dangereuse ou angoissante. Cependant, il n'en est pas toujours ainsi et des manifestations de peur ou d'angoisse peuvent se rencontrer chez des pilotes jusque-là bien adaptés.

Il faut distinguer :

- des manifestations de peur réactionnelle qui surviennent dans des situations inhabituelles ou difficiles tenant aux conditions particulières du vol et de la mission ou à un état d'affaiblissement du sujet (fatigue opérationnelle, défaillance physiologique). Ces manifestations sont transitoires et cèdent facilement au repos.

- des manifestations anxieuses durables qui surviennent dans des conditions de vol normales et habituelles, qui se répétent et qui constituent alors les véritables phobies du vol.

II - LES ASPECTS CLINIQUES

1. GENERALITES

L'expression clinique de la peur du vol peut être

- manifeste d'emblée : elle est alors ressentie et décrite comme telle par le sujet. Ce sont les cas les plus rares.

- manifeste, mais son expression ne se fera que de façon progressive, le sujet s'efforçant de masquer et de minimiser ses difficultés. Il n'exprimera ses troubles qu'après un certain temps de répétition des malaises et au terme d'une véritable lutte contre les sentiments pénibles qu'il éprouve.

- le plus souvent, la peur en vol sera latente. Elle ne s'exprime pas comme telle, mais à travers des manifestations symptomatiques variables prenant soit l'aspect de troubles d'allure somatique, soit l'aspect de troubles du comportement professionnel et relationnel.

Le mode de début est variable

- soit brutal sous la forme par exemple d'un malaise en vol survenant de façon soudaine chez un pilote sans aucun trouble antérieur ;

- soit de façon progressive et insidieuse par des troubles d'abord minimes et transitoires et qui vont peu à peu devenir de plus en plus intenses et permanents après une évolution de plus ou moins longue durée.

Des facteurs déclenchants ou favorisants de ces troubles sont souvent retrouvés à l'examen. Il s'agit d'événements concernant la vie professionnelle ou la vie personnelle et affective. L'importance et le rôle d'un événement ne tiennent pas tant à sa réalité objective, mais bien davantage à sa valeur subjective dont la signification psychopathologique ne pourra être appréciée qu'après plusieurs entretiens psychologiques.

Les circonstances d'apparition peuvent être diverses, mais les troubles vont survenir parfois lors de certaines missions ou lors de certaines configurations particulières du vol : haute ou basse altitude, vol en formation, vol sans visibilité, etc... D'abord limités à ces circonstances particulières, les troubles vont s'étendre progressivement à toute forme d'activité aérienne, voire à d'autres moyens de transport ou de déplacement (automobile, train) ou d'autres situations (phobies sociales).

2. LES FORMES CLINIQUES

1) Les formes à expression somatique prédominante

- Le malaise en vol en représente le tableau le plus spectaculaire et le plus typique avec ses manifestations fonctionnelles aiguës suffisamment intenses pour perturber ou interrompre une mission. Il associe le plus souvent des troubles neuro-sensoriels, une altération de la vigilance voire une obnubilation ou une perte transitoire de conscience, des manifestations douloureuses, respiratoires, cardio-vasculaires ou digestives, à un sentiment d'angoisse parfois très intense. Ils s'observent surtout dans l'aviation de chasse où les contraintes physiologiques sont prépondérantes, mais se rencontrent aussi dans les autres types de pilotage. L'approche psychologique des malaises en vol est toujours nécessaire quels que soient les facteurs étio-pathogéniques en cause. En effet, ou bien le malaise est l'expression d'une manifestation phobique du vol ou bien il peut représenter le point de départ de manifestations anxieuses ultérieures, le sujet redoutant de voir réapparaître le malaise lors des prochains vols.

- sans atteindre l'intensité du malaise en vol, d'autres troubles d'allure somatique peuvent s'observer en vol. Il s'agit surtout de manifestations sensorielles (visuelles, auditives ou des vertiges) ou des troubles fonctionnels à type d'impotence avec sensations douloureuses (crampes, douleurs musculaires, pseudo-paralysies, etc...). Le caractère transitoire de ces troubles, leur répétition, l'absence d'atteinte organique les font considérer comme des réactions de conversion de type hystérique. Leur appréciation est souvent difficile et délicate et nécessite la répétition des examens et la collaboration de divers spécialistes. Les pilotes victimes de ces troubles récusent au moins au début toute participation émotionnelle ou psychologique et convaincus d'être atteints d'une affection somatique s'insurgent devant la négativité des examens et la consultation psychiatrique.

Les manifestations du mal de l'air sont l'apanage des élèves-pilotes et sont très rares chez les pilotes confirmés.

2) Les formes à expression anxieuse

Elles comportent un syndrome psychique qui réalise un état de tension pénible et douloureux avec sentiment d'insécurité, d'attente et de pressentiment d'un danger à venir (peur de perdre le contrôle de soi-même, de perdre connaissance, de mourir, de devenir fou), une attitude d'hypervigilance, d'attention exagérée vis-à-vis des perceptions venant de l'environnement ou de soi-même, avec difficultés de concentration et de réaction.

Des manifestations somatiques de l'angoisse peuvent s'y associer :

- dyspnée, palpitations, douleur ou gêne thoracique ;
- sueurs, tremblements, secousses musculaires ;
- nausées, douleurs abdominales ;
- sensation de chaleur ou de froid ;
- étourdissements, vertiges, instabilité psycho-motrice.

Ces manifestations anxieuses peuvent rester limitées à certaines situations ou bien s'étendre progressivement et prendre une forme de plus en plus obsédante qui vient assaillir le pilote en dehors de la situation : peur de provoquer un accident et d'entraîner les autres dans la mort par exemple.

3) Les troubles névrotiques après accident aérien

Il faut distinguer :

- les réactions émotionnelles immédiates après l'accident, manifestations anxieuses à l'idée rétrospective d'avoir frôlé la mort, mais plus souvent état d'excitation et d'euphorie à l'idée d'avoir échappé à l'issue fatale.

- les réactions plus tardives qui vont associer à l'anxiété des sentiments à la fois d'agressivité et de culpabilité en particulier quand l'accident dont le sujet se sent responsable a fait des victimes.

L'accident peut porter atteinte au sentiment d'intégrité professionnelle et d'invulnérabilité du pilote. Il peut entraîner un doute et un sentiment d'incertitude sur ses aptitudes et ses capacités. Certains sujets expriment parfois nettement l'impression d'"avoir été trahi" par eux-mêmes, par l'avion ou par l'institution aérienne et perdent en tout ou en partie leur sentiment de confiance professionnelle.

Enfin, dans quelques cas, après un temps de latence, peut se constituer une véritable névrose traumatique avec son syndrome caractéristique de répétition de l'événement traumatique qui envahit la vie psychique diurne et nocturne.

4) Les troubles du comportement

Certains pilotes n'expriment pas leurs troubles sur un mode somatique ou psychique mais vont attirer l'attention par des modifications de leur comportement.

- Troubles du comportement professionnel : réticence à voler, refus de certaines missions, sous des prétextes divers, vérifications excessives avant et pendant le vol, missions écourtées, incidents en vol, pannes fréquentes dont l'origine ne peut être démontrée au sol,attitude de repli et de retrait vis-à-vis des autres membres du groupe aérien.

- Troubles du comportement général : le plus fréquent et le plus banal est la fatigue. Il s'agit d'une fatigue durable, qui peut céder au repos mais réapparait dés que le pilote reprend les vols. La fatigue s'accompagne d'insomnie, de rêves pénibles, de cauchemars, d'irritabilité, d'une consommation excessive et inhabituelle de tabac, d'alcool ou de médicaments.

5) Evolution

Dans ce contexte, peuvent survenir des incidents, voire un accident aérien, des erreurs professionnelles, parfois des fautes disciplinaires. C'est dire l'intérêt et l'importance d'un dépistage précoce de la part du médecin, des camarades et des responsables de la formation aérienne. En effet, peu à peu le pilote perd l'estime de lui-même et des autres, se sent dévalorisé et peut constituer un véritable état dépressif avec idées suicidaires.

III - LES FACTEURS ETIO-PATHOGENIQUES

- Les facteurs prédisposants :

Il faut évoquer rapidement les déficits adaptatifs, c'est-à-dire le cas de sujets dont l'adaptation aéronautique n'a jamais été bien satisfaisante, dont l'apprentissage a été long et laborieux et dont l'histoire professionnelle a toujours été émaillée de difficultés. Les troubles ici sont en continuité avec les difficultés antérieures et relèvent d'une insuffisance d'apprentissage et d'un défaut d'adaptation.

Quand il s'agit de pilotes jusque là bien adaptés professsionnellement et sans troubles antérieurs, on peut évoquer le rôle prédisposant d'une motivation étayée sur une organisation névrotique de la personnalité qui était jusque là bien compensée. A l'occasion d'un facteur favorisant ou déclenchant, une décompensation va se produire dans l'organisation de la personnalité et de la motivation professionnelle aboutissant à un conflit névrotique dont l'activité professionnelle est l'enjeu. Le vol est alors l'objet de sentiments ambivalents à la fois négatifs et positifs. La phobie du vol est alors directement issue de ce conflit névrotique. Ces mécanismes psycho-pathologiques sont particulièrement nets dans les organisations contra-phobiques qui conduisent les sujets à rechercher activement destsituations qu'ils redoutent inconsciemment au lieu de chercher à les éviter.

Des motivations conflictuelles peuvent se rencontrer dans d'autres modes d'organisation de la personnalité. On peut aussi formuler l'hypothèse que la motivation aéronautique est au départ toujours conflictuelle. C'est alors l'importance du conflit psychique ou sa réactivation à l'occasion des aléas de la vie affective et professionnelle qui est déterminante dans l'apparition des manifestations phobiques.

- Les facteurs favorisants :

Il s'agit de facteurs qu'on pourrait qualifier de "surcharge" susceptibles de solliciter de façon excessive les moyens adaptatifs du sujet et de fragiliser ses mécanismes de défense : activités opérationnelles intensives entraînant surmenage et fatigue ; mauvaise ambiance collective ; difficultés de relation et de communication dans le groupe aérien ; et bien sûr toutes les difficultés personnelles, affectives ou somatiques.

- Les facteurs déclenchants :

Il est fréquent dans l'examen psychologique des sujets atteints de phobie du vol de mettre en évidence des événements particuliers fortement investis affectivement et qui semblent jouer le rôle de véritables facteurs déclenchants des troubles.

Il s'agit :

- soit d'événements à caractère personnel : mariage, paternité, deuils, divorce, échecs affectifs ou sexuels, affection somatique.

- soit d'événements à caractère professionnel : mutation, promotion, prise de responsabilités nouvelles, changement d'appareil ou de type de mission. Incident ou accident aérien.

C'est la signification symbolique et subjective de l'événement qui importe et le remaniement qu'il provoque dans l'économie psychique du sujet. Ainsi une atteinte somatique portant atteinte à l'intégrité physique et la perception habituelle de bonne santé, vient remettre en cause le sentiment d'invulnérabilité. Le mariage, la paternité, peuvent déplacer les investissements affectifs de la vie professionnelle à la vie familiale. Un deuil, un accident peuvent réactiver une angoisse de mort latente.

La valeur pathogène de l'événement est souvent difficile à établir et à apprécier. Mais le plus souvent tout se passe comme si, du fait ou à cause de cet événement, l'équilibre des forces psychiques sur lequel reposait l'adaptation professionnelle se trouve modifié.

PRONOSTIC

D'une façon très schématique, on peut opposer au plan de la pratique et du pronostic, deux modalités dans les manifestations phobiques du vol chez les aviateurs confirmés.

- Les réactions phobiques qui sont des manifestations transitoires et limitées, qui font suite souvent à un événement vécu comme traumatique dans l'instant mais qui ne remettent pas en cause gravement l'organisation de la personnalité et de l'adaptation professionnelle des sujets, et joue un simple rôle de déconditionnement transitoire.

- Les phobies du vol organisées, évoluant parfois depuis plusieurs mois qui traduisent un remaniement important et conflictuel de la motivation aéronautique et dont le pronostic apparaît alors beaucoup moins favorable.

IV - LES ASPECTS THERAPEUTIQUES

- Le traitement préventif

Le recrutement, la sélection. Comme pour tous les troubles de l'adaptation aéronautique, la prévention des troubles commence dés les modalités du recrutement et de la sélection initiale des candidats pilotes. Il convient d'éliminer les sujets présentant des troubles psychopathologiques dans leurs antécédents et les personnalités fragiles. Mais les méthodes de sélection ont leurs limites. Ces limites tiennent à l'âge des sujets dont les motivations et la personnalité ne sont pas encore toujours bien affirmées et également au caractère statique et limité de la sélection initiale du fait du nombre de sujets à examiner. Il est donc nécessaire que la sélection se poursuive lors de la formation et de l'apprentissage aérien dans les écoles de pilotage.

Prévention et hygiène mentale au sein des unités navigantes

La bonne cohésion du groupe aérien, un moral élevé, la qualité des relations interpersonnelles jouent un rôle évident et essentiel dans l'hygiène mentale collective. La préparation des missions, une cadence des vols soutenue mais préservant un repos suffisant et nécessaire, des activités de détente et de loisirs organisées en commun ("les dégagements"), la bonne connaissance des caractéristiques personnelles de chacun, de ses possibilités et de ses limites sont des principes bien connus du commandement qui en assume la responsabilité.

Le Médecin d'unité peut dans ce domaine jouer un rôle essentiel. Bien intégré au groupe, connaissant personnellement chacun, il peut susciter et recueillir les confidences, prodiguer des conseils et jouer un rôle d'intermédiaire informel et de médiateur indispensable à l'écart des modalités habituelles des relations hiérarchisées.

- Le traitement curatif

Face à un pilote en difficulté, le médecin d'unité devra comprendre souvent à demi-mot la signification des troubles présentés. Il pourra permettre l'expression verbale des difficultés, apporter un soutien moral et parfois médicamenteux, prescrire le repos nécessaire. Des troubles mineurs, dépistés de façon précoce, trouveront ainsi souvent leur solution au sein même de l'unité.

Devant des troubles caractérisés, des examens spécialisés permettront d'établir un bilan soigneux qui précisera le mode de début, les circonstances d'apparition, la durée et les modalités d'évolution, les caractéristiques de l'adaptation antérieure et de la personnalité des sujets et la qualité de leurs motivations.

Au plan du traitement, on préconisera :

- le repos et la mise à l'écart d'une situation stressante ;

- un traitement anxiolytique médicamenteux ;

- des entretiens à visée psychothérapique qui permettront l'expression et la verbalisation des conflits éventuels ;

- des techniques de relaxation et de déconditionnement spécifique qui peuvent parfois se révéler efficaces.

Le maintien du sujet au sein de son unité navigante sera discuté. Si le maintien est souhaitable devant des troubles mineurs susceptibles de se résoudre rapidement, la mutation est parfois préférable pour éviter une mise à l'écart et une dévalorisation possible d'autant que le groupe aérien peut se montrer facilement intolérant à un de ses membres qui n'assume plus les mêmes activités et responsabilités et donne l'impression de ne plus partager le même idéal commun à voler. Des solutions intermédiaires pourront être trouvées avec l'aide du médecin d'unité et des autorités.

Les décisions médico-aéronautiques permettront de restreindre les missions et en limitant l'aptitude médicale de préconiser la reconversion dans une autre activité aéronautique.

Si dans certains cas l'apparition de phobies du vol conduit rapidement à l'inaptitude, il faut parfois un long travail psychothérapique pour faire accepter au sujet son ambivalence pour le vol et les changements intervenus dans ses motivations à exercer son activité professionnelle.

REPORT DOCUMENTATION PAGE

1. Recipient's Reference	2. Originator's Reference	3. Further Reference	4. Security Classification of Document
	AGARD-CP-415	ISBN 92-835-0414-3	UNCLASSIFIED

5. Originator Advisory Group for Aerospace Research and Development
North Atlantic Treaty Organization
7 rue Ancelle, 92200 Neuilly sur Seine, France

6. Title

BIOCHEMICAL ENHANCEMENT OF PERFORMANCE

7. Presented at

the Aerospace Medical Panel Symposium held in Lisbon, Portugal from 30 September to 2 October 1986.

8. Author(s)/Editor(s)	9. Date
Various	March 1987
10. Author's/Editor's Address	**11. Pages**
Various	136

12. Distribution Statement This document is distributed in accordance with AGARD policies and regulations, which are outlined on the Outside Back Covers of all AGARD publications.

13. Keywords/Descriptors

Flight crews
Performance
Fatigue
Drugs
Nerve cells

14. Abstract

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Major advances are being made in areas dealing with regulation of neuronal reponsiveness. This offers a number of opportunities for exploring the ways in which the biochemistry of the neurons may be altered, in a reversible way, to increase their responsiveness to neurotransmitters and/or other agents. Human performance may therefore be enhanced through these alterations.

The agents which initiate the change in neurone responsiveness may be supplied through nutrition, pharmaceuticals or biochemicals. This symposium considered the use of pharmaceuticals to promote sleep, increase vigilance and to alter regulatory centres. Neurotransmitter precursors were supplied via nutritional supplements.

AGARD Conference Proceedings No.415
Advisory Group for Aerospace Research and Development, NATO
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Printed by Specialised Printing Services Limited
40 Chigwell Lane, Loughton, Essex IG10 3TZ

ISBN 92-835-0414-3