MIDAZOLAM: AN IMPROVED ANTICONVULSANT TREATMENT FOR NERVE AGENT-INDUCED SEIZURES

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ABSTRACT

The drug midazolam has been recommended to replace diazepam as the immediate anticonvulsant treatment for nerve agent-induced seizures. This recommendation marks the latest decision in an ongoing program to improve medical countermeasures to treat nerve agent poisoning. Extensive rodent screening studies first identified midazolam as the most promising compound to focus on for advanced testing. Midazolam was then evaluated directly with diazepam for the ability to terminate nerve agent seizures in a nonhuman primate model. In all animal tests midazolam was twice as potent and more rapidly acting than diazepam, thus minimizing the possibility of seizure-induced brain damage.

INTRODUCTION

In November of 1990 the U.S. Army fielded the anticonvulsant drug diazepam in the Convulsant Antidote, Nerve Agent (CANA) autoinjector for the immediate field treatment of nerve agent-induced seizures. Each CANA injector contains 10 mg of the drug diazepam. Military personnel are issued one CANA injector in addition to the three MARK 1 antidote kits, each of which contains autoinjectors of atropine (2 mg/injector; total = 6 mg) and the oxime 2-PAM Cl (600 mg/injector; total = 1800 mg). The diazepam in the CANA injector is to be administered by the casualty's buddy or a medic at the onset of severe effects from a nerve agent (when the casualty's condition warrants the use of three MARK 1's at the same time), whether or not seizure activity is among the effects. Additional CANA autoinjectors are available to the combat medic to treat severely poisoned individuals; the medic is authorized to give up to two more 10-mg injections of diazepam to convulsing casualties (total allowed dose = 30 mg diazepam).[1]

The fielding of CANA marked the end of research and development efforts that first started in the early 1980's. At that time it was already recognized that diazepam and other benzodiazepine-type drugs provided significant improvements in preventing the lethal effects of nerve agent exposure when used as an adjunct treatment in conjunction with the standard anticholinergic and oxime therapy. Then came reports that exposure to nerve agent, primarily soman, produced brain lesions in survivors of intoxication.[2,3,4] Throughout the mid-1980's researchers investigated the three most prevalent hypotheses that were advanced to account for this brain pathology: a direct neurotoxic effect of the agent, the result of brain hypoxia/anoxia/ischemia coincident with the effects of acute intoxication, or the result of prolonged seizures triggered by the agent intoxication. Numerous studies were performed to evaluate these different hypotheses, and by 1987 it had been concluded that the brain damage was primarily the result of prolonged seizure activity that was triggered by intoxication by the agent.[5] Some of the major studies contributing to this conclusion were those that showed that treatment of animals with diazepam or other benzodiazepine

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anticonvulsant drugs, in conjunction with the standard atropine and oxime therapy, minimized or prevented the development of brain lesions as well as enhanced survival following nerve agent exposure.[6,7,8,9,10,11]

By the late 1980s it was decided that anticonvulsant protection against nerve agent-induced seizures was critical for complete therapeutic protection of nerve agent casualties.[12] The logical drug to develop at that time was diazepam. It was the drug most frequently used in nerve agent protection studies and was already approved for clinical use by the U.S. Food and Drug Administration (FDA) with an indication for treatment of status epilepticus seizures. Diazepam was a significant improvement over previous medical defense capabilities since it provided the ability to deliver immediate anticonvulsant treatment that may stop or minimize the neurotoxicological effects of nerve agent-induced seizures.

However, experimental findings showed that diazepam may not be the optimal compound for anticonvulsant protection against nerve agent-induced seizures. First, while diazepam reduced the incidence and severity of neuropathology in nerve agent-intoxicated animals, the protection was never complete.[6, 7,11,13] Secondly, it was found in primate models that the dose of diazepam needed to control soman-induced convulsions might be greater than first estimated.[11,14,15] Finally, there were continuing concerns from clinicians that the IM route of dosing would not achieve therapeutic levels of diazepam sufficient to stop seizures.

In addition to doubt about the sufficiency of diazepam, research studies showed that at least two other classes of drugs exerted strong control of nerve agent-induced convulsions and seizures. Drugs that act as antagonists of the glutamate receptor, in particular the N-methyl-d-aspartate subtype and to a much lesser extent the AMPA subtype, proved to provide substantial protection against nerve agent-seizures and brain damage.[16,17,18,19,20] In addition, antimuscarinic anticholinergic drugs with strong central activity also produced robust anticonvulsant effects against nerve agent-induced seizures.[21,22,23,24,25] These findings contributed to a growing realization that there were still gaps in our understanding of the basic neuropharmacological mechanisms of nerve agent seizures and the production of neuropathology and raised the question of the suitability of diazepam as the best anticonvulsant treatment for nerve agent-induced seizures. In reaction to these questions, the development of an advanced anticonvulsant treatment was formally adopted as an Army Science and Technology Objective (STO) in 1993.

1. INITIAL ADVANCED ANTICONVULSANT DEVELOPMENT RESEARCH EFFORTS.

In the 1993-1995 time frame, the major research efforts were arrayed along five lines. First, the standard drugs used clinically to treat epilepsy or seizure disorders were evaluated for the potential to moderate nerve agent-induced seizures. This work showed that, with the exception of the benzodiazepines (diazepam and midazolam) and barbiturates, the standard antiepileptic drugs were unable to stop ongoing nerve agent seizures.[26] Secondly, there were a variety of compounds that different authors had championed as being capable of stopping or moderating nerve agent seizures (e.g., memantine, clonidine) that had been evaluated by observational procedures only. Additionally, there were a number of research discrepancies based on the animal model and/or the procedure used to evaluate anticonvulsant effectiveness (i.e., observation vs EEG) that needed resolution. Close evaluation of several drugs that exerted a purported anticonvulsant effect against nerve agent seizures showed that these were primarily due to a profound muscle relaxation (e.g., memantine, neuroactive steroids; EEG seizures were still evident) or required such a narrow dose range or specific treatment conditions that development of them as a field treatments would be impractical (e.g., clonidine, huprazine, ivermectin; worked over narrow dose range and only as pretreatments). Other studies showed differences in the anticonvulsant effectiveness of diazepam and centrally acting anticholinergics depending upon the animal model used; both failed to produce an anticonvulsant effect in rat when given 40 min after seizure onset, whereas they did in a guinea pig model. The third major thrust was to evaluate in greater depth the contribution of the glutamatergic system to nerve agent seizures, nerve agent-induced brain damage, and the therapeutic potential for use of antiglutamate drugs to antagonize these effects. These studies showed that antagonists of the AMPA subtype of the glutamate receptor produced very weak anticonvulsant effects by themselves.[26] Evaluation

of compounds that acted as antagonists at the NMDA subtype of the glutamate receptor showed they produced robust anticonvulsant activity against nerve agent seizures, but this class of compounds had several drawbacks that will be discussed in more detail below. The fourth major effort was to evaluate the potential antiglutamatergic properties of a variety of potent, centrally acting, anticholinergic drugs that had shown robust anticonvulsant activity in a rat nerve agent seizure model. This study showed that a number of anticholinergics possess NMDA antagonist activity at high doses and thus had dual therapeutic effects against nerve agent seizures[27]. Finally, a thorough review of the literature was performed and a review paper that evaluated and synthesized this broad research area was prepared. It was presented in an abbreviated form at the NATO RSG-3 meeting in Porton Down in 1995, and after undergoing a series of revisions, it was published.[5] This review has provided a theoretical framework within which to direct development efforts of anticonvulsant treatments as well as possible neuroprotectant drugs.

2. FOCUSING OF ADVANCED ANTICONVULSANT RESEARCH EFFORTS – DOWN-SELECTION OF CANDIDATE COMPOUNDS.

By 1995-1996, research showed that only three classes of drugs exerted strong anticonvulsant activity against nerve agent seizures: benzodiazepines, anticholinergics, and NMDA antagonists. At that point a decision was made to no longer concentrate on NMDA antagonists (e.g., MK-801, TCP, phencyclidine) for development as immediate field treatment of nerve agent seizures. Although these compounds had shown marked anticonvulsant activity against nerve agent-induced seizures as well as seizures produced by other experimental manipulations, they had several drawbacks that would make ultimate development very difficult if not impossible. NMDA antagonists are potent psychomimetic compounds, at high doses they are capable of producing morphological damage to brain neurons,[28] and, despite intense development efforts of several major drug companies, no drug of this class has been approved for human use by the FDA with the exception of ketamine.

At this time we were also performing studies to compare the anticonvulsant therapeutic efficacy of a variety of anticholinergic drugs against the current standard, diazepam. Ultimately, 11 anticholinergic compounds were investigated using a guinea pig model. Unlike previous results using rats[22,26], most of the tested anticholinergics were effective when given either shortly (5 min) or after a substantial delay (40 min) following seizure onset. However, the doses needed to achieve an anticonvulsant effect when treatment was delayed (40 min following seizure onset) were almost a log unit greater than those required of the same drugs when treatment was given shortly after exposure[29]. This indicated that there was a narrow therapeutic treatment window for producing an anticonvulsant effect with clinically relevant doses of anticholinergic drugs. The results also showed (again, unlike previous results with rats) that diazepam continued to produce anticonvulsant effects at equivalent doses when given either shortly or delayed after seizure onset. However, the anticonvulsant action of diazepam given IM in the guinea pig was very slow (~50 min) and required high doses of the drug. The implications of these results were that anticholinergics most likely could never serve as the sole anticonvulsant treatment for nerve agent-induced seizures since in most operational situations it could not be guaranteed that all casualties would receive immediate treatment. It was decided to investigate whether other benzodiazepine drugs had the same broad therapeutic activity as diazepam, and whether some may have a more rapid time to effect following IM dosing. Five benzodiazepines (avizafone, clonazepam, loprazolam, lorazepam, midazolam) were then tested using the guinea pig model.[30] The results of that study showed that all tested benzodiazepines showed equal efficacy (equivalent ED50s and latencies to seizure control for each compound) when given at 5 or 40 min after seizure onset. However, there were differences in potency of the different drugs, and there were marked differences between drugs in how rapidly seizures were controlled following IM injection. Of the compounds tested, midazolam had the "best" therapeutic profile – it was about twice as potent as diazepam and was the most rapidly acting compound of the drugs tested. These initial results were available for the Milestone 0 meeting in July 1997.

3. MILESTONE 0.

The Milestone 0 meeting is a programmed decision point in the development process where proof of concept is demonstrated. In attendance are the scientific proponent, the MRICD science and technology coordinator; the commander of the U.S. Army Medical Research and Material Command; the U.S. Army Medical Material Development Activity, the agency with ultimate responsibility to perform advanced development of a medical product; the Army Medical Department Center and School, the combat developer that sets doctrine (policy) as to how medical items are to be used; and a representative of Army Logistics, to determine the logistic support requirements of proposed new items.

The Milestone 0 meeting for the advanced anticonvulsant was held in July 1997. A summary of the scientific information to date reiterated much of what was discussed above. In short, both midazolam and several potent anticholinergic drugs (biperiden, scopolamine, trihexyphenidyl) appeared to be viable candidates for development.   It was decided at that point that an advanced anticonvulsant could reasonably be achieved and the program then entered a concept development phase with midazolam as the lead candidate compound. A target date of FY00 was established for the Milestone 1 review of this project. In addition, specific exit criteria were established that delineated goals/tasks that needed to be met/accomplished to consider that Milestone 1 had been achieved. These exit criteria are listed below.

Exit Criteria:
1. Identify one preparation to be recommended to the MS1 review body for transition.
2. Determine metabolism and distribution of compounds/preparation either by reference to existing literature or by conduct of appropriate nonclinical studies.
3. Provide sufficient pre-clinical (animal and any relevant human experience with similar compounds) data to permit a preliminary assessment of the safety and efficacy of the identified preparations.
4. During Phase 0 a scientific committee will identify valid surrogate endpoints, present valid support for these endpoints, and develop a plan for getting the product through FDA review.
5. A Scientific Steering Committee will consider all possible side effects from the use of these compounds.
6. Preparation of a Transition Information Paper suitable for use in development of an Investigational New Drug application for submission to the FDA.
7. Coordinate with the Combat Developer to insure availability of a draft Operational Requirements Document (ORD) containing a milestone schedule.
8. Perform an administrative review of any patent issues.

4. CONCEPT DEVELOPMENT – NONHUMAN PRIMATE STUDIES.

Following the accomplishment of the Milestone 0 review, the major research activity involved the development of a nonhuman primate model of nerve agent exposure and seizures to evaluate the anticonvulsant effectiveness of midazolam in comparison with diazepam.[31] The key features of this model were to faithfully approximate the field medical doctrine for use of pretreatment (pyridostigmine) and therapy (atropine and 2-PAM Cl) drugs, evaluate and document seizure control using EEG recording, and to concurrently determine blood levels of treatment compounds to estimate human dose levels. In this study, male rhesus monkeys were surgically prepared with cortical electrodes and a transmitter that allowed for continuous telemetry monitoring of EEG activity. On the day of exposure the animals were pretreated IM with 0.024 mg/kg pyridostigmine, which achieved ~25% inhibition of red blood cell cholinesterase at the time of exposure. At 42 min after pyridostigmine the animals were challenged with 15 ug/kg, IM, of the nerve agent soman ($2 \times LD_{50}$) and 1 min later were treated with 0.10 mg/kg (diazepam study) or 0.20 mg/kg (midazolam study; 3 diazepam treated animals), IM, atropine and 25.7 mg/kg, IM, 2-PAM Cl. The pyridostigmine dose produced cholinesterase inhibition equivalent to that provided by pyridostigmine pretreatment tablets, and the doses of atropine and 2-PAM Cl were mg/kg equivalent doses provided by 3

MARK 1 antidote kits to a 75 kg human. All animals developed EEG seizure activity in 5-9 min following exposure. One min after the appearance of epileptic EEG activity, individual animals were treated with one of two doses of diazepam, 0.40 or 0.63 mg/kg, or one of two doses of midazolam, 0.18 or 0.32 mg/kg, IM. Following diazepam or midazolam treatment, serial blood samples were taken to determine drug pharmacokinetics. Treatment with the 0.40 mg/kg dose of diazepam (N = 8) either failed to terminate EEG seizure activity (N=6) or failed to do so in a clinically relevant time frame (N=2). Treatment with the 0.63 mg/kg dose of diazepam (N = 6) terminated seizure activity (X ~ 70 min). Three animals recovered normally; in the other 3 animals the seizures returned after 2-3 hr. Diazepam pharmacokinetic estimates show that the 0.40 mg/kg dose produced a mean maximum plasma concentration of 202 ng/ml with a time to maximum concentration of 21.37 min, while the 0.63 mg/kg dose produced a mean maximum plasma concentration of 415 ng/ml with a time to maximum concentration of 18.80 min. With midazolam treatment, the 0.18 mg/kg dose failed to control seizures (N=3), while the 0.32 mg/kg dose rapidly stopped seizures (X = 32 min) in all animals tested (5 permanently, 1 temporally). Determinations of midazolam plasma pharmacokinetic estimates showed that the 0.18 mg/kg dose produced a mean maximum plasma concentration of 167 ng/ml with a time to maximum concentration of 28.4 min, while the 0.32 mg/kg dose produced a mean maximum plasma concentration of 195.6 ng/ml with a time to maximum concentration of 18.5 min. The results showed that the current recommended maximum field dose of diazepam (0.40 mg/kg) was insufficient to stop seizures induced by soman in a clinically meaningful time. Although the 0.63 mg/kg dose of diazepam could terminate soman-induced seizures, the time for seizure control was slow. Midazolam terminated seizures at a lower dose and more rapidly than diazepam. With both drugs, seizures could reoccur after a period of anticonvulsant effect, and if seizures were not completely terminated the animal never regained consciousness.

This study shows that the dose of diazepam needed to terminate ongoing nerve agent-induced seizures had been underestimated and that the maximum allowable dose needed to be increased by at least 50% to produce a reliable anticonvulsant effect. These doses are concordant with blood levels of diazepam reported clinically to control status epilepticus seizures[32] and correspond to doses that were reported to be effective in treating sarin- and VX-induced seizures in patients of the Japanese terrorist attacks.[33,34,35] In addition, the time it took to terminate seizures in the nonhuman primate model following diazepam injection was >1 hr, and in 2 of 5 animals the seizures recurred 1.5-2 hr following an initial period of anticonvulsant effect. In contrast, midazolam was effective in terminating seizures at roughly half the dose necessary for diazepam, the time for seizure termination was ~30 min, and seizure activity recurred in only 1 of 6 animals.

5. CONCEPT DEVELOPMENT: GUINEA PIG STUDIES AND OTHER ACTIVITIES.

Concurrent with this nonhuman primate work, two other rodent studies were performed. First, midazolam was evaluated in parallel with diazepam for ability to stop seizures produced by all threat nerve agents (GA, tabun; GB, sarin; GF, cyclosarin; GD, soman; VX; VR, the Russian analog of VX).[36] The results show, much like previous studies, that midazolam was both significantly more potent and rapidly acting than diazepam in controlling seizures elicited by each of these threat nerve agents. A second study evaluated combination treatments of the benzodiazepines (diazepam or midazolam), along with one of the anticholinergic drugs (biperiden, scopolamine, trihexyphenidyl) for controlling soman-induced seizures.[37] Results from the combination study showed that either of the two benzodiazepines could be paired favorably with the anticholinergics, and there was strong evidence of anticonvulsant synergism especially when treatment was delayed (40 min) after seizure onset. In addition to these laboratory efforts, an exhaustive review of the clinical epilepsy literature was performed and identified 32 published studies where midazolam was used to treat status eiplepticus or serial seizures. Midazolam successfully controlled seizures in 89% (506 of 568) of the reported cases, and the success rate was virtually identical when the drug was given IM (92% 168 of 182 cases).

6. MILESTONE 1 – TRANSITION TO ADVANCED DEVELOPMENT.

All this information, especially the data from the nonhuman primate study, solidified the decision to transition midazolam to advanced development. Midazolam acts by the same mechanism of action as diazepam. It is an FDA approved drug with a substantial history of safe use. In addition to its efficacy in treating nerve agent-induced seizures in both rodents and nonhuman primates, midazolam also has a documented history of use in the clinical treatment of status epilepticus. All these features, along with other administrative scientific tasks that were being performed concurrently with the experimental efforts, met the established exit criteria and culminated in the successful Milestone 1 review in early Sep 00.

Product development is guided by the U.S. Army Medical Material and Development Agency. The science and technology coordinator and Scientific Steering Committee continue to address scientific issues that arise as this development process goes on. Within the immediate future the major effort will involve pre-investigational new drug (IND) meetings with the FDA to outline research findings to date and explore the most effective way to have midazolam approved for treatment of nerve agent-induced seizures. This will be the most critical aspect of the development process because, unlike the development of other types of drugs, clinical efficacy trials cannot be performed against nerve agent-induced seizures in humans. Animal data will have to suffice for demonstration of efficacy against nerve agents.

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