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THE EFFECTS OF DECABORANE ON CEREBRAL ELECTRICAL ACTIVITY AND LOCOMOTOR BEHAVIOR IN THE CAT

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13. ABSTRACT

Central nervous system effects of decaborane administered intraperitoneally in cats were evaluated electrophysiologically and in runway performance tests. It was found that overt behavioral and physiological manifestations of toxicity from this compound appeared at doses of 1 mg/kg and above. These included depression of activity, general emesis, and weight loss. Runway performance showed significant disruption at doses of 0.5 and 0.25 mg/kg. Marked individual variation was observed in the effects of exposure on performance at these low doses. Decaborane was found to be similar to MMH and UDMH in the rapid onset of behavioral disturbance at low doses. However, differences were observed between these compounds in that no seizure manifestations were noted with decaborane and recovery from behavioral disruption required at least several days. In the latter regard, decaborane more closely resembled hydrazine in its behavioral effects.

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FOREWORD

This research was initiated by the Toxicology Branch, Toxic Hazards Division, Aerospace Medical Research Laboratory, under Project 7163. Experiments were performed under Contract AF F33615-69-C-1441 by the Department of Anatomy and the Brain Research Institute, School of Medicine, University of California, Los Angeles, California 90024.

The experiments were conducted jointly by M. D. Fairchild, PhD, of the Veterans Administration Hospital, Long Beach, California, and M. B. Sterman, PhD, of the Veterans Administration Hospital, Sepulveda, California. Kenneth C. Back, PhD, was contract monitor for the Aerospace Medical Research Laboratory.

This technical report has been reviewed and is approved.

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SECTION I

INTRODUCTION

The current use of the boron hydrides as high energy fuels with the attendant danger of accidental human exposure to these highly reactive chemicals has provided the need for obtaining basic information regarding their interaction with various biological systems.

Reports of human intoxication (Lowe and Freeman, 1957) with one of the boron hydrides, decaborane, and of disruption of operant conditioning tasks (Reynolds et al., 1964) and electrographic patterns (Delgado et al., 1963) in primates with this compound indicate that the central nervous system is one of the earliest and most profoundly affected organ systems. The work outlined in this report examines the effects of low, relatively nontoxic doses of decaborane on the locomotor performance of the cat, a parameter which has been demonstrated to be very sensitive to disruptive influences on the central nervous system by other high energy fuels of the hydrazine type (Sterman and Fairchild, 1967; Sterman et al., 1969).

SECTION II

METHODS

Utilizing procedures standardized in previous investigations (Sterman et al., 1969, 1972) two groups of animals were studied in two independent experimental paradigms, termed "static" and "dynamic" testing, respectively.

Static testing consisted of a screening of physiological and behavioral responses to intraperitoneally injected doses of decaborane. Eight animals were evaluated with doses ranging from 1-4 mg/kg. Animals were prepared surgically with indwelling electrodes placed stereotaxically into various brain structures and sutured into muscle tissues to provide for monitoring of brain electrical activity and peripheral physiological variables. Following recovery from surgery animals were adapted to a large experimental chamber and connected through a suspended cable system to a 10-channel Grass Model 78 polygraph.

On test days behavior was classified together with continuous physiological recording for a period of at least 3 hours prior to drug administration. Observation and recording continued for 5-6 hours following decaborane injections. Animals were then returned to the home cage and standard observations were obtained daily until all overt symptoms disappeared. These included weight, food and water consumption, and amount and texture of excrements, as well as behavioral assessment.

In the dynamic testing 6 male adult cats were trained to stable performance in a special runway apparatus. Integrated behavior was quantitated by measurement of the time required to run, alternately, between two enclosed chambers. This apparatus and its application in the study of centrally acting chemical compounds have been described elsewhere (Fairchild and Sterman, 1964, 1965; Sterman and Fairchild, 1967; Sterman et al., 1969). Briefly, trained animals were maintained at 85% of normal weight and brought daily in predetermined order to the runway laboratory for 1-hour test periods. The runway apparatus consisted of two identical chambers separated by a plank suspended over a water trough. Animals were trained to perform in this apparatus for milk, in accordance with the automatically programmed operation of its components. Relays associated with chamber doors and photoelectric cells, placed at various points in the path between chambers, operated timing devices which allowed performance to be segmented and expressed precisely in terms of velocity. Experimental sessions consisted of 40 sequential trials in which the animal ran alternately between chambers.

In the present experiment, a previously utilized, counterbalanced design was initiated for evaluation of decaborane effects upon performance. This design called for daily trials in which the effects of three doses of decaborane could be determined and related to time after administration. Doses selected were 0.50, 0.25, and 0.125 mg/kg of decaborane, diluted with corn oil and administered intraperitoneally. These dose levels were chosen as a result of findings in the previously described static testing studies.

Testing was organized into three phases. The first involved five days of sequential sessions in which normal saline was administered intraperitoneally several hours before testing. All injections were administered at the same time each day, and the animals were tested hourly in predetermined order following administration.

The second phase followed immediately on the first, such that a dose of 0.5 mg/kg decaborane was administered on the 6th test day in place of saline. Performance data were collected in the normal manner on that day and on successive days until all manifestations of drug effects had disappeared from runway behavior in all animals. Saline injections were not utilized during this period. Testing with saline was reinitiated after the animals had returned to control performance and continued for five consecutive days, after which the second dose of decaborane (0.25 mg/kg) was evaluated.

The same postdrug procedures were utilized, involving daily monitoring until disappearance of symptoms and a saline control period. Testing of the third dose (0.125 mg/kg) was then initiated, with identical follow-up procedures. The overall experiment consisted of 64 consecutive days of evaluation. Performance was assessed daily, except for weekends, in the initial phase of study. A suspension of testing occurred from the 47th day through the 53rd day due to an equipment failure. The animals were carefully observed during this period, and daily body weights and food and water consumption were measured. Both wet and dry foods were available in the home cage. During the entire study daily notes were made concerning the animals' overall condition as indicated by behavior, amount and character of feces and urine, and presence or absence of vomitus.

SECTION III

RESULTS

1. STATIC TESTING

A. Gross Behavior and Toxicity

Table I summarizes the results obtained in 8 adult male cats injected intraperitoneally with decaborane in doses ranging from 1-4 mg/kg. Lethargy and hypoactivity occurred at all doses tested, and acute vegetative symptoms (emesis, defecation, urination) with subsequent weight loss appeared at 2 mg/kg. One fatality occurred within 24 hours following 2 mg/kg, but 3 and 4 mg/kg did not prove lethal in the two animals receiving these amounts. The animal which expired at 2 mg/kg exhibited gross hypoactivity and emesis but not defecation or urination during the 6-hour period of observation following injection. Since two animals survived at 3 and 4 mg/kg following more pronounced symptoms of acute poisoning, the relationship between decaborane toxicity and the single fatality is not clear.

As a result of these tests, 0.5 mg/kg decaborane was selected as the upper limit of dosage for the dynamic tests.

TABLE I. Summary of Gross Toxic Figures of Decaborane in the Adult Cat (Intraperitoneal Injections)

Test No.	Dose (mg/kg)	Gross Behavior Hypoactive	Vegetative Symptoms			Prognosis	
			Emesis	Defecation	Urination	Weight Loss	Death
1	1	x					
2	1	x					
3	2	x					
4	2	x		x	x	x	
5	2	x	x	x	x	x	
6	2	x	x				within 24 hrs
7	3	x	x	x	x	x	
8	4	x	x	x	x	x	

B. Electrographic Responses

Recordings of spontaneous brain electrical activity from numerous cortical and subcortical electrode sites throughout the neuraxis did not reveal any evidence of gross change attributable to decaborane. The electrographic records generally reflected the behavioral appearance of the animal, with larger amplitude slow waves dominant during periods of hypoactivity being replaced by normal desynchronized fast activity as the stress of vegetative effects produced by the drug became evident. In these studies of decaborane in the cat, with subcortical recording electrodes placed primarily in motor pathways and limbic structures, no evidence of localized electrical after discharge or bursts of high frequency activity was obtained with single dose administration. In the monkey, Delgado et al (1963) occasionally observed such patterns from hypothalamic and thalamic electrodes after repeated doses of decaborane.

II. Dynamic Testing

Intraperitoneal injections of decaborane at doses of 0.5 and 0.24 mg/kg in the cat can disrupt runway performance for a period of eight to ten days following administration. One of the most dramatic features of this effect was the large degree of individual variation displayed in 6 cats in terms of their sensitivity to the disruptive effects of decaborane on locomotor performance. This is demonstrated in the comparison between Figures 1 and 2 showing doses of decaborane in cat 1 and cat 6, respectively. The former animal was completely unresponsive to the compound, while the latter exhibited profound and long-lasting alterations in runway behavior which occurred in a dose-related manner. The body weight curves in both figures show that neither animal experienced major changes in body weight during the 64-day period of observation; this was true for all cats in the series.

Figure 3 represents the pooled data from all 6 cats where the large amount of variability in response is reflected in the magnitude of the standard error of the means. This is particularly true for the middle dose of 0.25 mg/kg where the contribution to the pooled effect is primarily derived from only two animals, both of which experienced major disruptions at this dose. Two cats showed minor alterations in locomotor performance at the lowest dose of decaborane tested (0.125 mg/kg). Saline injections had no apparent effect.

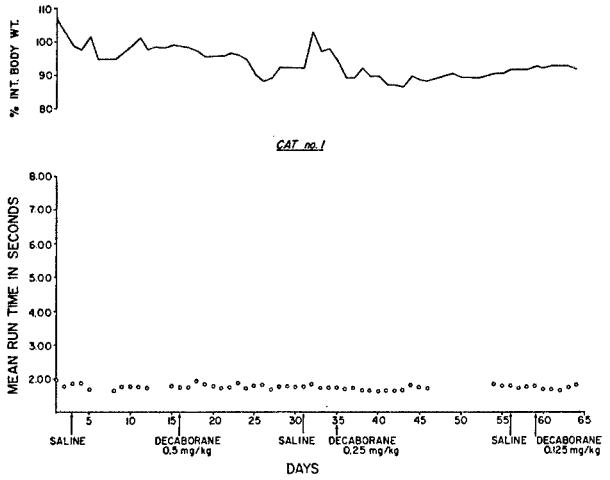

Figure 1. Runway performance and body weight data from cat No. 1 for 64 days of testing during the administration of saline and graded doses of decaborane. The open circles in the lower trace represent the mean run times for 40 sequential runway trials. Standard errors of the means are not plotted in this figure because their magnitude was insufficient for resolution. The lack of runway data between days 45 to 53 was due to equipment failure.

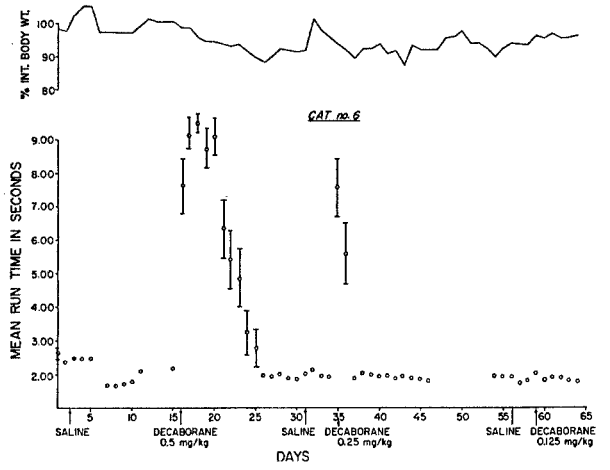

Figure 2. Runway performance and body weight data from cat No. 6 displayed as detailed in Fig. 1. Standard errors of the mean are plotted in the lower trace where resolution was possible.

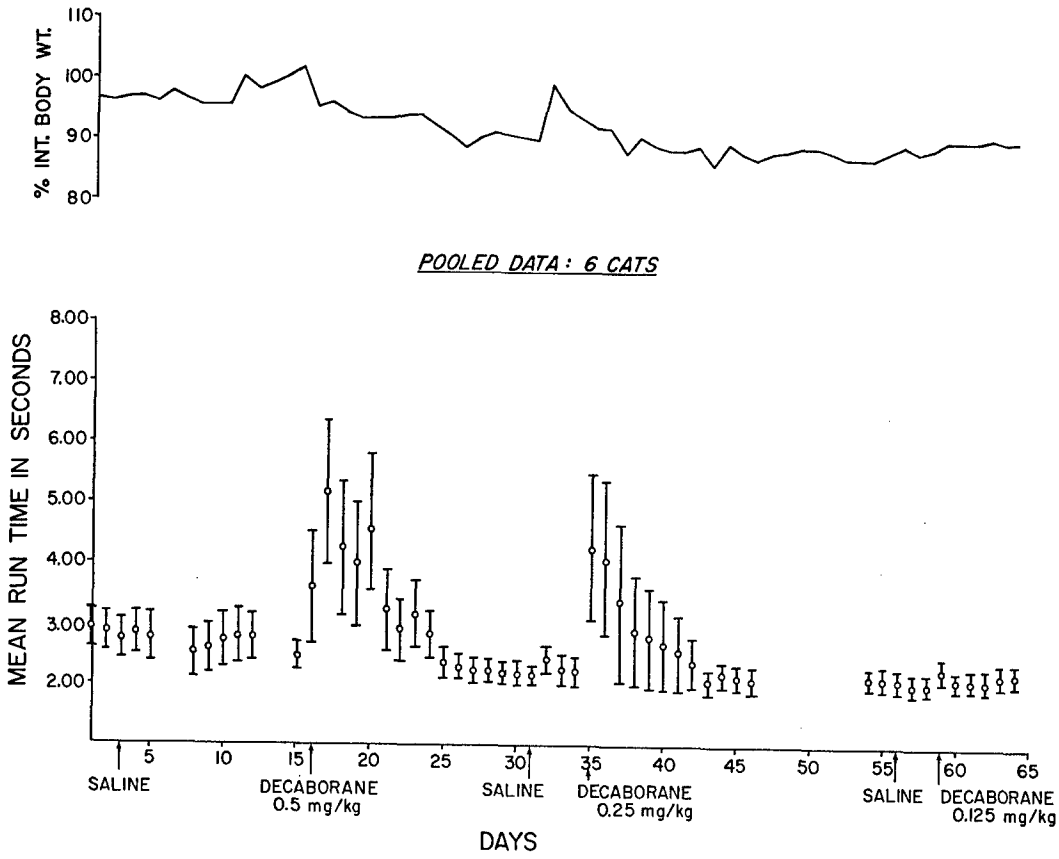

Figure 3. Runway performance and body weight data from the pooled data of the 6 cats utilized in this study displayed as detailed in Fig. 1. An examination of the data for time-dependent effects from 1 to 6 hours following injection was unremarkable. The drug reaction, when present, was evident within one hour post-injection and usually persisted for a matter of days rather than hours.

These results indicate that decaborne in doses between 0.25 and 0.50 mg/kg, which are sufficiently small not to produce symptoms of gross behavioral, nutritional or central electrographic change, are capable, nevertheless, of producing marked and long-lasting decrements in the locomotor performance of the cat. The effects of decaborane, however, appear to be highly variable in this species.

SECTION IV

DISCUSSION

Evaluation of the effects of intraperitoneally administered decaborane in cats indicated a clear cut depression of activity at a dose of 1 mg/kg and objective vegetative symptoms at doses of 2 mg/kg and above. Performance in a runway task was generally disrupted for a period of several days at doses of 0.5 and 0.25 mg/kg. The effects of intoxication at these lower doses showed a remarkable variability among animals, which was similar to that observed in comparable tests of hydrazine (Sterman et al., 1972).

No cortical or subcortical EEG abnormalities were observed, with the exception of a generalized cortical EEG slowing consistent with concurrent behavioral depression. Delgado and co-workers (1963) also reported behavioral depression from higher doses of decaborane administration in chronic monkey preparations. They frequently noted no EEG changes in association with this depression, an observation confirmed in the present study. Localized and propagated electrical seizures (originating mainly in the hypothalamus) were observed in one monkey following a dose of 1 mg/kg decaborane and in most animals after repeated daily injections of 1-2 mg/kg. The hypothalamus was not routinely monitored in the present study; nevertheless, no evidence of seizure discharge was obtained in 14 cats exposed through single administrations to doses ranging from 4 mg/kg to 0.124 mg/kg. A species difference in seizure threshold could account for this discrepancy. Other species differences in toxic response to decaborane have been reported by Krackow (1953).

Performance evaluation of decaborane in our runway apparatus proved to be a most sensitive index of drug effects. As reported, also, in a series of previous studies of various hydrazine compounds, this behavioral test disclosed a disruptive influence of decaborane at doses significantly below the level of overt symptomotology. In contrast to hydrazine, which produced a delayed disruption (Sterman et al., 1972), decaborane influences on runway performance were apparent within one hour of administration. In this regard, decaborane exposure more closely resembled the effects of monomethylhydrazine and unsymmetricaldimethylhydrazine. However, recovery from these hydrazine derivatives was relatively rapid, requiring only one or two days, whereas recovery from both hydrazine and decaborane was considerably longer.

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