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Arnold H. Maloney

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SODIUM N-METHYL-CYCLOHEXENYL-METHYL-BARBITURIC ACID (EVIPAL): HYPNOSIS, ANESTHESIA AND TOXICITY

A. H. MALONEY and R. HERTZ

Department of Pharmacology, Howard University School of Medicine, Washington, D. C.

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The sodium salt of N-methyl-cyclohexenyl-methyl-malonylurea (evipal) is one of the most interesting of the newer barbituric acid compounds. While it exhibits a rapid and high hypnotic coefficient and a very short duration of action, its toxicity, provided that it is properly administered, is considerably lower than that of the so-called short-acting barbiturates, e.g., nembutal, pernocton, and amytal. In these respects evipal bears closer resemblance to diethylepoxy-propionamide, diethylepoxy-methylpropionamide and other epoxy amides being elaborated by Fourneau, Billeter and Bovet (1) than it does to the better known and more widely employed barbiturates.

The enormous amount of literature appearing in recent months indicates that evipal has gained considerable popularity as a general anesthetic in surgical procedures of short duration. This popularity is due to its wide margin of safety, speed of induction, good relaxation, minimal disturbance of circulation, short duration and negligible after-effects. However, very little work has been reported from the laboratories. Because of this paucity of basic data we deemed it expedient to subject this new barbiturate to certain pharmacological tests. The present report is limited to data obtained in studies of the hypnotic, the anesthetic, and the toxic action of evipal on rats and rabbits.

TECHNIQUE

With the exception of one series of 10 rats, treated subcutaneously for the purpose of determining the differential absorb-
tion and utilization rate by different modes of administration, all our records were taken on the effects of the compound administered intraperitoneally. This latter mode of administration was selected because we have found from extensive experience that while the rate of absorption and the effects produced are practically the same as by the slow intravenous method advised and employed for clinical use, it obviates variabilities which result from the possible inconstancy of injection rate by the intravenous route.

All animals were deprived of food for twenty-four hours before treatment. At the time of injection each was weighed and given its dose based on milligrams per 100 grams of body weight for the rats and milligrams per kilogram for rabbits. But for uniformity the doses are all translated to milligrams per kilogram in table 1. To insure greater accuracy in the rat experiments a tuberculin syringe was used. No animal was employed more than once in this study. Mature stock albino rats all obtained from the same breeder, and stock rabbits ranging from 1500 to 2300 grams were employed.

As evipal is very unstable when in solution it was freshly prepared for each seance. A 5 per cent aqueous solution was used.

THE RAT

We used as criterion for hypnosis the technique employed by Nielsen, Higgins and Spruth (2). At intervals of five minutes a bit of straw was gently introduced into the external auditory meatus and the onset and duration of hypnosis were determined by the time of abolition and restoration, respectively, of the reflex response to tickling. In some instances hypnosis was induced with doses of 20 and 30 mgm. (all doses in this paper represent milligrams per kilogram of body weight) but it was only at 40 mgm. that the majority of animals in a series of 10 gave positive responses. At 50 mgm. all animals in the series gave positive responses. Hypnosis began five minutes (figures on time are all averages for each series of 10 animals) following injection and lasted twenty-five minutes. We regard this latter dosage as the minimal effective hypnotic dose for the rat. As the
dosage increased the average time of onset of hypnosis was reduced and the duration was extended. Thus with 60 mgm. hypnosis came on in three minutes and lasted thirty-five minutes; at 80 mgm. it came on in two minutes and lasted forty-five minutes. In the series (mentioned above) where evipal was given subcutaneously, 100 mgm. produced narcosis in nineteen and one-half minutes enduring for twenty-five minutes. By the subcutaneous route the rate of absorption is comparatively slow.

Surgical anesthesia was obtained in the dosage ranges beginning at 60 mgm. However, at this level the duration of action was rather short for practical consideration, the average time being four minutes. At 80 mgm. surgical anesthesia lasted ten minutes. When the dose was increased to 100 mgm. excellent anesthesia with good relaxation was obtained. Hypnosis occurred within two minutes; and this passed on to surgical anesthesia in ten minutes, which lasted twenty minutes. Recovery was rapid and no ill effects seemed to follow awakening. No fatalities occurred within this series. We regard 100 mgm. as the minimal effective anesthetic dose.

For studies of toxicity the dose was stepped up from 100 to 150 mgm. and since only one death resulted from this latter dose it was deemed unnecessary to try intervening amounts for such studies. The table shows a fairly regular linear curve of toxicity. The M.L.D. was found to be 280 mgm. At this dose 5 of 10 animals died. As a further check one series was given 290 mgm. and the result showed 7 deaths out of 10. Expressing the M.L.D. as one hundred, the toxic-anesthetic-hypnotic ratio would be 100:36:18. This represents a high coefficient of effectiveness. By comparison 60 per cent of the M.L.D. of nembutal, pernocton or amytal is required to produce anesthesia, Fitch and Tatum (3), whereas 36 per cent of either compound would be merely within the range of mild hypnosis.

RABBITS

Ten animals were used in each of three series and given doses of 50, 60, and 70 mgm. in each series. The results are summarized as follows: 50 mgm. of evipal injected intraperitoneally was
adequate to produce effective surgical anesthesia in the minority of this series. Hypnosis came on four minutes (these figures represent the average) after the injection and lasted twenty-five minutes. The duration of deep anesthesia varied between zero and fifteen minutes. Sixty milligrams produced hypnosis three minutes after injection which lasted for a period averaging forty-four minutes. The duration of deep anesthesia was from five to twenty-five minutes. A few animals in this series also manifested some degree of tolerance to the drug, failing to develop profound narcosis. Seventy milligrams induced hypnosis in most instances within two minutes and deep anesthesia within five minutes which lasted thirty-five minutes. These animals remained asleep for an average of one hour and twenty minutes. All recovered. This was taken as the effective anesthetic dose for the rabbit.

For studies on toxicity 100 mgm. was given to each of a series of 10 with no fatalities. At 150 mgm. of a series of 6, 2 died within nine minutes after the injection; 4 recovered. At 200 and 250 mgm., respectively, 2 out of a series of 3 each died within one minute after the injection. The actual M.L.D. is still undetermined. The number of rabbits available was not quite adequate for the completion of this phase of our investigation.

### TABLE 1

Toxicity studies on rats; evipal 5 per cent intraperitoneally

<table>
<thead>
<tr>
<th>SERIES</th>
<th>DOSE (mgm./kgm.)</th>
<th>SURVIVED</th>
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<tr>
<td>1</td>
<td>100</td>
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<tr>
<td>2</td>
<td>150</td>
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<tr>
<td>3</td>
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<td>10</td>
<td>290</td>
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</table>
DISCUSSION

Kennedy (4) has described the anesthetic action of evipal on mice, rats, guinea pigs and frogs. Kennedy and Narayana (5) have reported on the effect of evipal on the heart action in the frog, on blood sugar, temperature, respiration and blood pressure on rabbits, rats, cats and guinea pigs. Maloney (6) has compared the efficiency of evipal in cocaine intoxication with other barbiturates. Jackson (7) has demonstrated its antagonism to metrazol on the dog. These reports represent all the work on animal subjects with evipal which we have found in the literature.

The response of the animal to evipal is striking. There is a fall in blood pressure and synchronously, respiration becomes slower and shallower. These phenomena always occur when an intravenous injection is being made too rapidly regardless of the quantity given. In this event the animal may die from sudden respiratory failure. The kymographic record of such an event shows a horizontal straight line on the respiratory writing point with a vigorous rise in the magnitude and height of the pressure tracing lasting for some few minutes before a gradual fall and terminal stoppage. This indicates that the death is unquestionably respiratory in character. Sudden death is easily avoidable if the intravenous injection is slowly timed or if some other mode of administration is employed.

With an optimally safe rate of absorption one observes the following characteristic behavior: The animal shows an apprehensiveness which may border on excitement. Rats may be seen to paw vigorously at the nose with the front legs until these members cease to be active while rabbits may often scream and start. Insidiously there comes on a loss of coördination traveling from the hind limbs cephalad. The animal is definitely ataxic (a condition especially noticeable in the dog) until he finally falls over on his side. In this position an appreciable number of rats will show a mild degree of opisthotony. This has not been observed in the rabbit or dog. Many animals manifest gross tremors; dogs and rabbits may even have a frank shiver indicating disturbance of the heat-regulating mechanism. The respiration which at the beginning is frequently irregular or jerky now
becomes regular but markedly slow and shallow. Finally all gross reflexes are abolished, provided the dose is adequate. With the induction of anesthesia relaxation is complete. As anesthesia begins to wear off there is a rapid reverse recapitulation of the above-described phenomena.

The speed with which the body reacts to the administration of evipal is remarkable. The toxicity curves here presented are based upon a uniform mode of administration. We feel certain that the intraperitoneal route is by far more accurately representative of the slow intravenous method than that method itself; for even in the hands of a single operator variations in rate might occur which would be adequate to vitiate results. The hazard of toxicity is inherent not in the drug per se but rather in its absorption constant in the system in any unit of time. The detoxifying mechanism can cope adequately with a vast quantity of the compound spread over a relatively long period of time whereas it may easily be overwhelmed by a mere fraction of that same amount if absorbed in a moment.

Rapidity of disposal runs parallel with speed of utilization. Delayed death of an otherwise healthy animal from evipal is not demonstrable. If the animal does not succumb to a given dose ten or twelve minutes after it is given intravenously or intraperitoneally that animal will survive. Safety and therapeutic efficiency are consequently functions of rate and degree of absorption and detoxification. In critical cases of intoxication with evipal the immediate intravenous injection of picrotoxin is eminently life-saving. Depression which is not grave will be overcome spontaneously or recovery may be hastened with the use of metrazol or coramine.

There was substantial corroboration of results on all points where our investigations have been similar or identical in nature to those reported by the workers to whom we have referred in this paper.

SUMMARY

A study is made of the hypnotic and anesthetic action and the toxicity of evipal in rats and rabbits.
1. The optimal hypnotic dose is 50 mgm. per kilogram for the rat.
2. The optimal anesthetic dose is 100 mgm. per kilogram for the rat and 70 mgm. per kilogram for the rabbit.
3. The m.l.d. for the rat is 280 mgm. per kilogram; for the rabbit the exact figure was not determined.
4. This compound has a high coefficient of effectiveness. The toxic-anesthetic-hypnotic ratios in the rat being 100:36:18.
5. Because of the uniformity of results the intraperitoneal method of administration was employed.
6. The response of the animals to evipal intoxication is described.

REFERENCES

(1) Fourneau, Billeter and Bovet: J. de Pharmacie et de Chimie, 19, 49, 1934.
(2) Nielsen, Higgins and Spruth: J. de Pharmacie et de Chimie, 14, 523, 1931.