THE EFFECT OF BETA, BETA-METHYLETHYLGLUTARIMIDE (MEGIMIDE) AND THIOPENTAL IN DOGS

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The discovery that \( N \)-allylnormorphine is a specific antagonist to morphine gave hope that something might be discovered or developed which would have a similar antagonism to barbiturate depression. A report by Shaw et al. (1) indicated that \( \beta \), \( \beta \)-methylethylglutarimide (Megimide) might be a barbiturate antagonist. Early reports, although they seemed to indicate definitely that \( \beta \), \( \beta \)-methylethylglutarimide was effective in offsetting barbiturate anesthesia were characterized by lack of adequate experiments. Further reports (2, 3, 4) threw doubt on the efficacy on this drug because the awakening did not seem to be nearly so dramatic as that following the use of \( N \)-allylnormorphine. Another factor to be considered is that in clinical barbiturate poisoning pentobarbital has usually been ingested whereas thiopental is the drug most frequently used in the operating room. It therefore seemed advisable to measure the effect of \( \beta \), \( \beta \)-methylethylglutarimide given after doses of thiopental.

METHODS

Experiments were carried out using two groups of 5 dogs each. Thiopental was administered in single intravenous doses to all 10 dogs in quantities sufficient to produce surgical anesthesia. Loss of both medial and lateral canthus reflexes was the criterion used for adequate depth of anesthesia. Approximately 20 mg./kg. were required by each dog. Five of the animals were then given \( \beta \), \( \beta \)-methylethylglutarimide intravenously in amounts that were 50 per cent of the quantity of thiopental used. The dose was therefore approximately 10 mg./kg. The \( \beta \), \( \beta \)-methylethylglutarimide was injected over a period of one minute beginning one minute after the injection of thiopental was completed. The recovery time of each animal was recorded, judged (a) by elapsed time at which the dog raised his head spontaneously and (b) by time elapsed when the dog rose on all four legs.

After allowing at least a week to elapse in order to avoid the possibility of tolerance to thiopental, the experiments were repeated with the difference that the 5 animals that had received only thiopental the first time now received thiopental plus \( \beta \), \( \beta \)-methylethylglutarimide, and those that received both drugs originally now received only thiopental. After at least another week, the experiments were again repeated and the drug order was again reversed, that is, the third

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group of experiments was identical with those of the first week. Identical quantities of thiopental were used in each dog each of the three weeks, although the quantities varied, of course, from animal to animal. This type of cross-over experiment was designed to allow each dog to be his own control, and to eliminate any effect that might possibly ensue from giving the thiopental before the combination of thiopental plus β, β-methylethylglutarimide or vice versa.

RESULTS

Table 1 presents the results obtained. The waking times the third week were not significantly different from those measured the first week when the same doses of the same drugs were administered. This was true whether thiopental alone was administered first or whether thiopental plus β, β-methylethylglutarimide had been administered first.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dog Number</th>
<th>Recovery Time</th>
<th>Drug</th>
<th>Recovery Time</th>
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<tr>
<td></td>
<td></td>
<td>Head Up (min.)</td>
<td>All Fours (min.)</td>
<td>Head Up (min.)</td>
<td>All Fours (min.)</td>
<td>Head Up (min.)</td>
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<tr>
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<td>14</td>
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<tr>
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<tr>
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<td>5</td>
<td>11</td>
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Average Recovery Time Thiopental Alone
15 Administrations
Head Up 32.5 minutes A
All Fours 46.3 minutes B

Average Recovery Time Thiopental + Megimide
15 Administrations
Head Up 19.3 minutes C
All Fours 28.9 minutes D

Critical Ratio
A - C = 2.1
B - D = 2.6
It may be assumed therefore that the order of carrying out the experiments did not affect the results and that no tolerance to thiopental developed.

It will be seen that the average recovery time as measured by lifting the head was 32.5 minutes when thiopental alone was given but that giving thiopental plus \( \beta \), \( \beta \)-methylglyutaramide shortened the time to 19.3 minutes. If one judges recovery time by the animals' rising to all fours, the corresponding values are 46.3 and 28.9 minutes. In these experiments then, \( \beta \), \( \beta \)-methylglyutaramide shortened the recovery time to about two-thirds what it would have been if \( \beta \), \( \beta \)-methylglyutaramide had not been administered.

**Discussion**

Clinical reports on the use of \( \beta \), \( \beta \)-methylglyutaramide have varied tremendously. Bentel, Barlow, and Ginsberg (5) state enthusiastically "Megimide brought about a rapid recovery of consciousness in all cases. Megimide is a direct antidote to thiopentone." This assertion may be compared with the guarded opinion expressed by Louw and Sonne (2) who state, "It seems that in severe cases coma must be expected to last for one to three days with or without Megimide." Kjaer-Larsen (6) observed that 16 of 50 patients treated with \( \beta \), \( \beta \)-methylglyutaramide had convulsions.

Several authors have stated that \( \beta \), \( \beta \)-methylglyutaramide had some analeptic effect but that the results were not dramatic. Plum and Swanson (7) used \( \beta \), \( \beta \)-methylglyutaramide in cases of human barbiturate poisoning and felt that the drug showed little evidence of true barbiturate antagonism although it seemed to possess nonspecific analeptic properties. Pedersen (3) observed an undoubted arousing effect in 22 cases of barbiturate poisoning but when he compared the time for regaining consciousness with that of 74 control cases who did not receive the drug, there was no appreciable difference. Louw and Sonne (2) stated that administration of \( \beta \), \( \beta \)-methylglyutaramide helped in stimulating reflex activity and respiration although it did not shorten recovery time. Clemmensen (4) believed that \( \beta \), \( \beta \)-methylglyutaramide and amiphenazole are valuable adjuvants in the treatment of acute barbiturate poisoning but that patients so treated did not regain consciousness until the blood level of barbituric acid had dropped to the same value as in patients who were not so treated.

The results of our own experimental work are in essential accord with the opinions shared by authors mentioned. \( \beta \), \( \beta \)-methylglyutaramide did cause some analeptic effect, but did not appear to be a rapid antagonist to thiopental.

**Summary**

Thiopental and thiopental plus \( \beta \), \( \beta \)-methylglyutaramide were administered alternately to each of 10 dogs in cross-over experiments
at least a week apart. Sleeping times as terminated by spontaneous lifting of the head or rising to all fours were noted. Each dog served as his own control. Sleeping time of dogs receiving thiopental plus β, β-methylethylglutarimide was about two-thirds that observed when the animals received thiopental alone. The results obtained indicate that β, β-methylethylglutarimide has an analeptic action rather than being a specific inhibitor of the action of barbiturates.

Francis Candlin, D.V.M., supplied the Megimide used in these experiments.

REFERENCES


NOTICE OF THE ANNUAL MEETING

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