THE MEDIAN LETHAL DOSE (LD₅₀) OF PENTOTHAL SODIUM FOR BOTH YOUNG AND OLD GUINEA PIGS AND RATS *†‡

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In 1934, Lundy and Tovell (1) reported on the use of a new derivative of the barbituric acid series, sodium ethyl l-methyl butyl thioarbituric acid, and referred to it as thionembutal. This drug was later named (2, 3) "barbiturate A" and more recently renamed (4) "pentothal sodium." Because of its short anesthetic action following intravenous administration, it was labeled an intravenous anesthetic agent and was not so thoroughly tested for its toxicity in laboratory animals by intraperitoneal administration as other barbiturates have been tested (5, 6, 7). Mulinos (8), however, administered pentothal sodium intraperitoneally to rats and reported that doses of 90 to 100 mg. per kilogram killed 60 per cent of the animals. Gruhzit et al. (9), using the same method of administration in rats, found that it took 100 mg. per kilogram of the drug to kill 60 per cent of the animals. Pratt et al. (10) reported that 80 mg. per kilogram of pentothal sodium killed 50 per cent of their rats when the drug was administered intraperitoneally.

Since only a few isolated tests on the toxicity of pentothal sodium by intraperitoneal administration had been reported, it was decided to make such a study, using a large number of both guinea pigs and rats. The results here reported represent studies of the median lethal dose of the drug for both young and old guinea pigs and rats. We have accepted Trevan's (11) interpretation of the median lethal dose as one that kills 50 per cent of the animals in a large series (LD₅₀).

EXPERIMENTAL DATA

Normal and well-fed stock guinea pigs and hooded rats were used in the experiments. Both males and nonpregnant females of each species were used.

The diet for the guinea pigs consisted of oats, alfalfa hay, lettuce and other green vegetables, and water. The rats had a diet of wheat.

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† A preliminary report of this work appeared in the Federation Proceedings 1: 13, 1942 and 2: 6, 1943.
‡ The pentothal sodium was kindly furnished by Abbott Laboratories, North Chicago, Illinois.
bread, corn bread, table scraps, whole corn, lettuce, whole milk and water. Green foods were not given the day the drug was administered. The animals were allowed the other foods and water *ad libitum* to within about one hour before receiving the drug.

A fresh 0.5 per cent aqueous solution of pentothal sodium was prepared previous to each series of injections. The solution was injected intraperitoneally through the flank with a blunt needle. All of the injections were made by the author, usually early in the day so that observations could be made over a long period. The doses varied by increments of 2.5 mg. per kilogram from 35 to 60 mg. for guinea pigs and they varied by increments of 5 mg. per kilogram from 100 to 130 mg. for old rats and from 90 to 140 mg. for young rats.

To study the effects of the drug, the periods of time required for the development of three stages in the hypnotic state were selected and recorded (5, 6, 7): (a) the time from the injection until the animal could not support and propel itself after stimulation either by gently pulling the hair on the hips or by pinching; (b) the time from the injections until the animal could be aroused sufficiently to walk or propel itself forward after stimulation, and (c) the time from the injection until the animal could walk with a steady gait for a distance of about a meter. Sleep began at the conclusion of the first stage. The time from the injection until the animal had awakened and was able to walk with a steady gait was considered as the maximal hypnotic time. The time of injection and the onset of sleep were recorded for all animals. The duration of sleep and the maximal hypnotic time were recorded for many of the animals that survived. In case an animal did not survive, the time that the heart ceased to beat was accepted as the time of death.

As soon as the animals were unable to walk, they were placed in an incubator at about 90°F. and kept there until they died or were able to walk. These experiments have extended over a period of slightly more than four years.

In order to study the effect of age on the toxicity of guinea pigs, three arbitrary weight groups were selected: 200 to 299 Gm., 300 to 499 Gm. and 500 to 1,015 Gm., with the first group being considered as young animals. The rats were selected according to two arbitrary age groups: those from a few weeks to 9 months old and those at least 12 months old.

The onset of sleep for guinea pigs varied from two to eight minutes, with an average of three to four minutes. The average duration of sleep and the maximal hypnotic time generally increased with an increase in the dose for the animals that survived. These values were not constant for a given dose. The average values for a 40 mg. dose are given as an example: (a) onset of sleep 3.79 minutes; (b) duration of sleep, 116 minutes and (c) maximal hypnotic time, 279 minutes. The duration of sleep often extended to as much as eight to ten hours with the large doses. If the dose was fatal, the animals usually died within thirty minutes to one hour, but some survived a few hours.
Four hundred and ninety-five guinea pigs were used and 202 of these were classed as young animals (table 1). Since guinea pigs increase in weight for several months after birth, the 293 old guinea pigs were divided into two weight groups, 300 to 499 Gm. and 500 to 1,015 Gm., to determine whether any difference in toxicity could be observed. The median lethal dose (LD₅₀) for young guinea pigs, weight group 200 to 299 Gm., seemed to be about 47.5 to 52.5 mg. per kilogram, while it seemed to be about 52.5 to 57.5 mg. for old guinea pigs.

**TABLE 1**

**STUDIES ON THE TOXICITY OF PENTOTHAL SODIUM FOR DIFFERENT WEIGHT-GROUPS OF GUINEA PIGS**

<table>
<thead>
<tr>
<th>Weight of Guinea Pigs</th>
<th>35</th>
<th>37.5</th>
<th>40</th>
<th>42.5</th>
<th>45</th>
<th>47.5</th>
<th>50</th>
<th>52.5</th>
<th>55</th>
<th>57.5</th>
<th>60</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young Guinea Pigs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 to 290</td>
<td>12</td>
<td>0</td>
<td>24</td>
<td>1</td>
<td>18</td>
<td>9</td>
<td>26</td>
<td>1</td>
<td>26</td>
<td>1</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>300 to 499</td>
<td>5</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>23</td>
<td>2</td>
<td>15</td>
<td>2</td>
<td>16</td>
<td>6</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Old Guinea Pigs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>500 to 1015</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>16</td>
<td>1</td>
<td>16</td>
<td>1</td>
<td>19</td>
<td>2</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>300 to 500</td>
<td>8</td>
<td>0</td>
<td>13</td>
<td>0</td>
<td>36</td>
<td>3</td>
<td>31</td>
<td>3</td>
<td>36</td>
<td>8</td>
<td>29</td>
<td>4</td>
</tr>
</tbody>
</table>

I, number of animals injected; D, number of animals that died following the corresponding injection of pentothal sodium.

* See text for explanation of doses.

The onset of sleep for rats usually occurred in two to three minutes. Both the duration of sleep and the maximal hypnotic time increased with the size of the dose, but they were less in each case with young animals than with the old animals. The duration of sleep for young rats ranged from eight to about twenty-seven hours. The maximal hypnotic time was usually at least one to three hours longer than the duration of sleep. The maximal hypnotic time for old rats that recovered usually was less than thirty hours, but 2 females were still unable to walk after forty-eight hours. If the dose was fatal, the animals usually died in less than two to five hours following the injection, but a few survived longer periods.

The series of rats included 365 animals; 280 of them were classed as young animals (table 2). The young rats were divided into three weight groups: 75 to 99 Gm., 100 to 199 Gm., and 200 to 380 Gm., to see whether there was any correlation between the small young animals and the larger animals of this group with respect to toxicity. The median lethal dose (LD₅₀) seemed to be between 120 and 135 mg. per kilogram for young rats and between 115 to 125 mg. for the old rats.
TABLE 2

STUDIES ON THE TOXICITY OF PENTOTHAL SODIUM FOR DIFFERENT WEIGHT-GROUPS OF YOUNG AND OLD RATS

<table>
<thead>
<tr>
<th>Weight of Rats</th>
<th>60</th>
<th>95</th>
<th>100</th>
<th>105</th>
<th>110</th>
<th>115</th>
<th>120</th>
<th>125</th>
<th>130</th>
<th>135</th>
<th>140</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young Rats</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>D</td>
<td>I</td>
<td>D</td>
<td>I</td>
<td>D</td>
<td>I</td>
<td>D</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>grams 75 to 99</td>
<td>10</td>
<td>2</td>
<td>10</td>
<td>2</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>6</td>
<td>11</td>
<td>71</td>
</tr>
<tr>
<td>grams 100 to 199</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>10</td>
<td>6</td>
<td>14</td>
<td>4</td>
<td>15</td>
<td>5</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>grams 200 to 380</td>
<td>2</td>
<td>0</td>
<td>7</td>
<td>2</td>
<td>10</td>
<td>2</td>
<td>10</td>
<td>3</td>
<td>12</td>
<td>4</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>grams 75 to 380</td>
<td>5</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>26</td>
<td>8</td>
<td>24</td>
<td>6</td>
<td>35</td>
<td>10</td>
<td>35</td>
<td>6</td>
</tr>
<tr>
<td>grams 220 to 566</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>13</td>
<td>4</td>
<td>13</td>
<td>6</td>
<td>13</td>
<td>5</td>
<td>15</td>
<td>12</td>
</tr>
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<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Old Rats</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>D</td>
<td>I</td>
<td>D</td>
<td>I</td>
<td>D</td>
<td>I</td>
<td>D</td>
<td>I</td>
<td></td>
</tr>
</tbody>
</table>

I, number of animals injected; D, number of animals that died following the corresponding injection of pentothal sodium.

* See text for explanation of doses.

COMMENT

Gruhzt et al. (9) used albino rats weighing 125 to 175 Gm., which correspond to the young rats in the second weight group (table 2). These authors, however, reported that 60 per cent of their animals died with a dose of 100 mg. per kilogram, while it took about 125 to 130 mg. to kill 50 per cent of the animals in the present study. The number of animals used was not given by either Gruhzt and co-workers or Pratt and co-workers, which may account for part of the differences in the results. Mulinos (8) reported that 9 of 15 rats died after administration of 90 to 100 mg. per kilogram of the drug, but did not state the age, strain or weight of the rats used. The diet of the animal may be a factor in its resistance to a toxic drug, as suggested by the studies on the toxicity of paraldehyde for rats by Phillips et al. (12).

From the data herein reported, it appears that the age factor should be taken into account when determining the toxicity of pentothal sodium in laboratory animals.

The LD₅₀ of pentothal sodium is higher than it is for nembutal (7) for the corresponding age and weight groups of rats. The LD₅₀ of nembutal was about 85 to 95 mg. per kilogram for old rats and about 100 to 120 mg. for young rats.

The LD₅₀ of pentothal sodium was less than it was for nembutal (5) for the corresponding lower weight groups of guinea pigs. The LD₅₀ for nembutal was 57.5 to 60 mg. for animals weighing 200 to 299 Gm. and 55 to 57.5 mg. for those weighing 300 to 499 Gm. The LD₅₀ with
nembutal for the heaviest weight-group, however, was about 47.5 mg. while the LD₅₀ with pentothal sodium for the same weight-group was about 57.5 mg. per kilogram.

SUMMARY AND CONCLUSIONS

The median lethal dose, LD₅₀, of pentothal sodium was found to be about 47.5 to 50 mg. per kilogram for young guinea pigs; 52.5 to 55 mg. per kilogram for older guinea pigs and about 57.5 mg. per kilogram for old guinea pigs, when injected intraperitoneally.

The median lethal dose, LD₅₀, of pentothal sodium was found to be about 125 to 130 mg. per kilogram for young rats and 115 to 125 mg. per kilogram for old rats, when injected intraperitoneally.

REFERENCES


THE NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS will meet in the Bigelow Amphitheatre, White Building, Massachusetts General Hospital, Boston, on Tuesday, December 9, at 8:00 P.M. The principal speaker will be Doctor F. A. Duncan Alexander, Chief of the Anesthesiology Section of Ashburn VA Hospital, McKinney, Texas, and Assistant Clinical Professor of Anesthesiology of Southwestern Medical Foundation, Dallas. Meetings of this organization are usually held on the second Tuesday of each month, with the exception of July and August.