CLINICAL STUDIES OF INDUCTION AGENTS

XXVII: THE RELATIONSHIP BETWEEN DOSAGE OF PROPANIDID AND DURATION OF SLEEP

BY

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SUMMARY

Studies have been carried out during induction of anaesthesia to relate the dose of propanidid to the duration of sleep. It was found that there was an almost linear relationship though the duration did not continue to increase in proportion to the dose. This differs from the expected relationship with thiopentone and seems to agree with the concept that propanidid is rapidly broken down in the blood stream.

It was shown by Dundee (1962) that the relationship between duration of anaesthesia and dosage of G.29.505 did not follow the relationship expected with the barbiturates but approximated to a straight line. A similar study has not been carried out on thiopentone but work by Dundee (1955), Keéri-Szántó (1960) and Clarke and Dundee (1966a) showed that the dose of thiopentone required to maintain a constant clinical level of anaesthesia over a prolonged period follows an exponential pattern. The last group of workers showed, on the other hand, that the requirements of propanidid did not fall off with time but followed the almost linear relationship expected from its method of breakdown.

Swerdlow and Moore (1967) have studied the relationship between dose of propanidid and awakening time after dental anaesthesia and found that it was almost linear over the narrow range of doses studied. The present work, carried out over several years, covers the whole range of clinical dosage of propanidid and was designed to investigate the exact relationship between duration and dosage from 0 to 15.5 mg/kg.

METHOD

The patients were females studied immediately before undergoing minor gynaecological surgery. They were premedicated with atropine 0.6 mg. The results were obtained in groups of 10 patients each, corresponding to each dose range of 1 mg/kg from 0.6–1.5 mg/kg to 14.6–15.5 mg/kg. The patients were all of physical status grades 1 and 2 (ASA classification) with ages ranging from 11 to 70. There was no selection with regard to the size of the dose each patient received. Since the maximum dose given was 1 g, however, none of the heaviest patients was included in the higher dosage groups. Propanidid was injected at a rate of 1 ml of the 5 per cent solution per 4 seconds and timing of sleep was from halfway through the injection to the moment when the patient opened her eyes in response to command. This method of timing the length of sleep differed from that of Dundee (1962), who gave G.29.505 more quickly and timed from the end of injection. Propanidid has a greater tendency to cause arterial hypotension than has the earlier eugenol derivative when injected in doses of the order of 4 mg/kg (Dundee and Clarke, 1964). In doses corresponding to 15 mg/kg it must be injected slowly if severe hypotension is to be avoided (Clarke and Dundee, 1966b). Because of the need to inject propanidid more slowly, it seemed preferable to start timing from the mid-point of injection. Nitrous oxide-oxygen was not given during the period of timing, but as soon as the patient opened her eyes a second injection was given and inhalation of nitrous oxide-oxygen started for the performance of the surgical procedure.

RESULTS

The findings from the 150 inductions of anaesthesia are shown in figure 1, in which duration of sleep is plotted against the dose of propanidid in mg/kg. There is clearly a marked correlation and a straight line could be drawn to fit these
Duration of sleep in 150 individual patients in relation to the dose of propanidid in mg/kg.

points. If the averages of the groups of 10 are plotted against dose, however (fig. 2), then the line of best fit is clearly not straight. The deviation shows that increasing the dose did not increase the duration of sleep proportionately.

The figures can be grouped in another way to determine the approximate dose required to produce sleep of a given duration (table I). The numbers in different duration groups varied widely but the most notable feature is the width of the range of doses in each duration group. It would therefore be quite impracticable to predict the amount of propanidid required to produce sleep of, say, 2–2½ minutes duration since the range of doses was 150–650 mg or 2.5–12.7 mg/kg. In fact, the figures suggest that there is no value, as regards estimation of expected duration of sleep, in giving doses on a weight-related basis because the range of doses in mg in each group is no larger than the range in mg/kg. It is also apparent that the longest duration of sleep likely to be encountered after a single dose is 6 minutes, and since this refers to the duration of sleep rather than surgical anaesthesia, the duration of the latter will be much less.

### Table I

<table>
<thead>
<tr>
<th>Duration of sleep (sec)</th>
<th>No. of patients</th>
<th>Dose range (mg)</th>
<th>Dose range (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No sleep</td>
<td>12</td>
<td>50–350</td>
<td>0.8–6.9</td>
</tr>
<tr>
<td>0–30</td>
<td>2</td>
<td>100–200</td>
<td>2.2–2.9</td>
</tr>
<tr>
<td>31–60</td>
<td>4</td>
<td>75–300</td>
<td>1.4–5.4</td>
</tr>
<tr>
<td>61–90</td>
<td>22</td>
<td>75–450</td>
<td>1.4–8.8</td>
</tr>
<tr>
<td>91–120</td>
<td>17</td>
<td>200–500</td>
<td>2.6–10.4</td>
</tr>
<tr>
<td>121–150</td>
<td>11</td>
<td>150–650</td>
<td>2.5–12.7</td>
</tr>
<tr>
<td>151–180</td>
<td>18</td>
<td>250–1000</td>
<td>6.0–12.3</td>
</tr>
<tr>
<td>181–210</td>
<td>15</td>
<td>350–825</td>
<td>6.5–15.0</td>
</tr>
<tr>
<td>211–240</td>
<td>20</td>
<td>350–850</td>
<td>4.0–14.9</td>
</tr>
<tr>
<td>241–271</td>
<td>16</td>
<td>500–1000</td>
<td>8.8–14.8</td>
</tr>
<tr>
<td>271–300</td>
<td>3</td>
<td>550–1000</td>
<td>8.6–14.6</td>
</tr>
<tr>
<td>301–330</td>
<td>6</td>
<td>650–1000</td>
<td>11.3–15.2</td>
</tr>
<tr>
<td>331–360</td>
<td>1</td>
<td>850</td>
<td>13.2</td>
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<tr>
<td>361–390</td>
<td>2</td>
<td>525–1000</td>
<td>9.7–13.7</td>
</tr>
<tr>
<td>391–420</td>
<td>1</td>
<td>1000</td>
<td>15.2</td>
</tr>
</tbody>
</table>
DISCUSSION

The finding that the duration of sleep after any intravenous anaesthetic increases with dose injected is to be expected but the exact relationship must depend on several factors: (1) the influence of the drug itself on the blood flow to and from the brain and other tissues; (2) the development of acute tolerance; (3) the rate of breakdown of the injected substance.

The work of Keéri-Szántó (1960) on thiopentone and the studies by Clarke and Dundee (1966) using intermittent dosage suggest that the duration would be expected to increase disproportionately with increasing dose. This could be due to the influence of this agent on the distribution of blood flow, blood reaching the brain rapidly but subsequent redistribution to the muscular tissues being delayed by cardiac depression and poor perfusion of the periphery (Price, 1960). It is known that thiopentone is only slowly metabolized and excreted, so that redistribution plays the major part in recovery (Brodie, 1952). However, the phenomenon of acute tolerance (Dundee, Price and Dripps, 1956) must act in the opposite direction because as the induction dose increases the blood level at which consciousness returns increases also. It seems likely that with thiopentone the other two factors are dominant.

Propanidid is rapidly broken down in the body to an inactive metabolite (Duhm et al., 1965; Wirth and Hoffmeister, 1965) and the results described here are in agreement with this. As the dose increases cardiovascular depression becomes more severe (Clarke and Dundee, 1966a) but this probably does not affect breakdown of propanidid in the blood in the same way as it affects the redistribution of thiopentone. The role of acute tolerance in recovery from propanidid anaesthesia has not yet been investigated because of the difficulty of taking samples quickly and preventing in-vitro breakdown of the drug.

The exact shape of the dose-duration curve should probably not be analyzed in detail because it must depend on the manner of injection. If the drug could be injected instantaneously and timing could begin from this point, exact analysis would be possible but since the injection rate is restricted by the toxicity of the drug the manner of timing is a compromise. The rate of injection adopted meant that the largest dose, namely 1 g, was administered over a period of 80 seconds and timing began after 40 seconds. It seems likely that if the drug is injected slowly and timing starts from the beginning of injection, the duration of sleep will be more prolonged than if the injection were instantaneous. This is the case because the latter fraction of the dose is only entering the circulation to be exposed to destruction when the first fraction has been already almost completely metabolized. If timing began from the end of injection the duration of sleep attributable to the initial fraction of the dose would not be included. The method of timing adopted here is, for these reasons, unlikely to give an answer far from the true one at the injection rate used.

The results reported by Swerdlow and Moore (1967), concerning the relationship of awakening time to the dose of propanidid injected, follow a pattern very similar to the present findings. These authors adopted a different injection rate, different criteria of awakening and a narrower dose-range (15–11 mg/kg). The curve obtained by them, if extrapolated to cross the zero time axis at a dose of about 1 mg/kg, is also slightly concave to the dose axis. Both sets of results, therefore, are in agreement with the view that propanidid is rapidly broken down in the body and behaves quite differently from thiopentone. Furthermore, the duration cannot be indefinitely prolonged by giving larger doses even if acute toxicity did not limit the dose given.

ACKNOWLEDGEMENTS

I am particularly grateful to Professor J. W. Dundee for help and advice throughout. Mr. P. J. Howard also gave most useful assistance with the timing. Thanks are due to my gynaecological colleagues at Musgrave Park Hospital for their co-operation in this study and to Dr. Donald Whitfield of Farbenfabriken Bayer A.G., who provided generous supplies of propanidid.

REFERENCES


**THE MIDLAND SOCIETY OF ANAESTHETISTS**

Programme for 1968/1969

Tuesday, November 26, 1968, at the Birmingham Dental Hospital.

6.30 p.m. Buffet.

7.45 p.m. Professor Cecil Gray, “The new syllabus for the Primary F.F.A.R.C.S.”

Thursday, March 13, 1969, at the South Staffordshire Medical Centre.

6.30 p.m. Buffet.

7.30 p.m. Registrars’ Papers.

Saturday, June 14, 1969, at the Queen Elizabeth Hospital, Birmingham, and the University Department of Anaesthetics.

General and All Day meeting of the Society. Detailed programme to be announced.