CLINICAL STUDIES OF INDUCTION AGENTS

XVII: RELATIONSHIP BETWEEN DOSAGE AND SIDE EFFECTS OF INTRAVENOUS BARBITURATES

BY

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SUMMARY

A retrospective analysis of the records of about 9,000 intravenous anaesthetics showed a striking relationship between dosage and induction complications. While the incidence of excitatory phenomena increased with dosage of thiobarbiturates, this effect was more marked with methylated barbiturates. The greater frequency of respiratory complications (cough, hiccough and laryngospasm) with high dosage was similar for both groups of drugs. Opiate premedications reduced the incidence of excitatory phenomena but had no effect on the respiratory complications. It is suggested that the "convulsive" element in the action of barbiturates predominates with higher dosage and the respiratory complications may be related to the action of the drugs on the parasympathetic nervous system.

It is now fairly well established that pre-anaesthetic medication is a major factor in determining the incidence and severity of complications during induction of anaesthesia with intravenously injected barbiturates. In a comprehensive investigation (Dundee, 1965) the dosage of barbiturates was kept constant for each drug studied and it was found that pre-anaesthetic medication with drugs shown to cause increased sensitivity to somatic pain, as assessed by the tibial pressure test, increased the frequency of spontaneous involuntary muscle movements and analgesic (opiate) premedication diminished the incidence.

In studies of a methylated thiobarbiturate Barron, Dundee and King (1961) showed that, when premedication was constant, dosage was a factor in determining the incidence of spontaneous muscle movements. In the case of methylated thiobutobarbitone (B.137), when atropine was used as sole premedicant 28 per cent of patients exhibited this complication with dosage of 2-4 mg/kg and this rose to 84 per cent when the dosage exceeded 8 mg/kg. Similar but less marked increases occurred with opiate premedication.

Dundee and associates (1961) have shown that these findings also apply to methohexitone; but with this drug the increase in induction complications with increasing dosage is not limited to muscle movements but also includes respiratory upset (cough and hiccough). With atropine premedication these combine to reduce the incidence of uneventful induction (grade I) from 70 per cent with doses of approximately 1 mg/kg to 12 per cent with doses in excess of 2.5 mg/kg; the comparable figures for opiate premedication were 85 and 48 per cent respectively.

Preliminary results reported by Barron (1964) suggested that all barbiturates behave in a similar, though quantitatively different, manner with respect to the effect of dosage. The present paper examines this hypothesis in more detail and reports on the relationship between dosage and the incidence of induction complications with four thiobarbiturates in current clinical use and also with two methylated barbiturates.

METHOD

Much of the data was obtained during the extensive comparison of thiopentone, buthalitone, hexobarbitone and thiamylal reported by Gilmore and Dundee (1962) and by Barron and associates (1966). In addition, data obtained from studies with thialbarbitone (Kemithal) are included and
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Table I

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Atropine</th>
<th></th>
<th>Opiate/atropine</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>Percentage excitatory phenomena</td>
<td>Percentage respiratory upset</td>
<td>Percentage grade I</td>
</tr>
<tr>
<td>under 3</td>
<td>706</td>
<td>9</td>
<td>0.4</td>
<td>93</td>
</tr>
<tr>
<td>3-4</td>
<td>744</td>
<td>11</td>
<td>2.2</td>
<td>82</td>
</tr>
<tr>
<td>4-5</td>
<td>559</td>
<td>9</td>
<td>4.3</td>
<td>73</td>
</tr>
<tr>
<td>5-6</td>
<td>318</td>
<td>9</td>
<td>4.1</td>
<td>84</td>
</tr>
<tr>
<td>6-7</td>
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<td>74</td>
</tr>
<tr>
<td>7-8</td>
<td>133</td>
<td>12</td>
<td>12.6</td>
<td>71</td>
</tr>
<tr>
<td>8+</td>
<td>70</td>
<td>27</td>
<td>11.4</td>
<td>53</td>
</tr>
</tbody>
</table>

Relating dosage of thiopentone to the percentage incidence of excitatory phenomena, respiratory upset and grade I induction, using both opiate and non-opiate premedication.

the final analysis makes use of published data concerning methohexitone (Dundee et al., 1961).

The cases are divided into two groups according to premedication; atropine only and atropine-opiate. (The choice and dose of preparation was left to the individual anaesthetist.) Dosage range varied widely according to the practice of the administrator. Data was provided by 25 anaesthetists who graded each case according to a prearranged scheme.

The observations following induction include the occurrence of:

- Excitatory phenomena: Tremor, spontaneous involuntary muscle movement or hyper-tonus.
- Respiratory upset: Cough, hiccup or laryngospasm.
- Marked respiratory depression: Requiring assistance.
- Hypotension: Fall in systolic blood pressure in excess of 20 mm Hg.
- Induction grade I: Uneventful.

Unfortunately the data on the hypotensive action of the drugs is too incomplete to justify detailed analysis.

RESULTS

Table I shows that with atropine premedication the percentage incidence of both excitatory phenomena and respiratory upset increases with increasing doses of thiopentone and this is reflected in the decrease in grade I (uneventful) inductions. The relationship between dosage and complications is less marked when an opiate was given as premedication, and the frequency of excitatory phenomena and respiratory upset becomes unduly high only with doses in excess of 8 mg/kg.

Thiamylal was used in fewer patients. The same trends were evident and figure 1 shows that the incidence of grade I induction decreases with increasing dosage. Thialbarbitone also behaves in a similar manner but the detailed results are not shown.

![Figure 1](image-url)
Buthalitone is normally followed by a higher incidence of cough and hiccup than thiopentone and figure 2 shows that the frequency of this complication is clearly related to dosage. This drug also follows the same pattern as thiopentone with respect to excitatory phenomena.

EXCITATORY PHENOMENA

RESPIRATORY UPSET

Incidence of excitatory phenomena and respiratory upset with differing doses of buthalitone.
- - - - atropine premedication (1108 cases). - - - - opiate-atropine premedication (388 cases).

Hexobarbitone is taken as the example of a methylated barbiturate and table II shows the findings with this compound. With or without opiate premedication, the incidence of excitatory phenomena increases markedly with dosage and, as might be expected, the frequency of this complication is less when opiates have been given. Respiratory complications also increase with dosage. It is important to note the very low incidence of uneventful inductions recorded after large doses of this drug.

Overall survey.

Data were pooled in order to ascertain the incidence of excitatory phenomena and respiratory upset with equipotent doses of all thiobarbiturates (thiopentone, thiamylal, buthalitone and thialbar-

**TABLE II**

*Relating dosage of hexobarbitone to the percentage incidence of excitatory phenomena, respiratory upset and grade I, using both opiate and non-opiate premedication.*

<table>
<thead>
<tr>
<th>Dose mg/kg</th>
<th>No. of cases</th>
<th>Percentage excitatory phenomena</th>
<th>Percentage respiratory upset</th>
<th>Percentage grade I</th>
</tr>
</thead>
<tbody>
<tr>
<td>under 4</td>
<td>104</td>
<td>39</td>
<td>0.8</td>
<td>63</td>
</tr>
<tr>
<td>4-6</td>
<td>184</td>
<td>36</td>
<td>1.6</td>
<td>74</td>
</tr>
<tr>
<td>6-8</td>
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<td>3.6</td>
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<td>8-10</td>
<td>132</td>
<td>50</td>
<td>5.3</td>
<td>40</td>
</tr>
<tr>
<td>10-12</td>
<td>101</td>
<td>64</td>
<td>8.9</td>
<td>32</td>
</tr>
<tr>
<td>12-14</td>
<td>82</td>
<td>76</td>
<td>3.7</td>
<td>21</td>
</tr>
<tr>
<td>14 +</td>
<td>96</td>
<td>73</td>
<td>13.5</td>
<td>24</td>
</tr>
<tr>
<td>Opiate/atropine</td>
<td>No. of cases</td>
<td>Percentage excitatory phenomena</td>
<td>Percentage respiratory upset</td>
<td>Percentage grade I</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>2</td>
<td>0</td>
<td>76</td>
</tr>
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<td></td>
<td>89</td>
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<td></td>
<td>44</td>
<td>50</td>
<td>11.4</td>
<td>41</td>
</tr>
</tbody>
</table>
bitone) and methyl barbiturates (methohexitone and hexobarbitone). The ratios of potency of the different drugs to thiopentone were taken as 1 for thiamylal, 0.5 for buthalitone, thialbarbitone and hexobarbitone, and 2.5 for methohexitone. Results expressed as equivalent doses of thiopentone. Thiobarbiturates were given to almost 6,000 patients and methylated barbiturates to 3,000.

No allowance was made for differing numbers of cases with different drugs in each group but those receiving an opiate premedication were considered separately from those who were given atropine only. The results with the thiobarbiturates are divided into groups with an adjusted dose range of 1 mg/kg, each group containing a minimum of 100 cases. Since the upper dose group with individual drugs comprises a wide range (e.g., 8+ mg/kg in table I can include doses ranging from 8 to 12 mg/kg), this is not included.

In figure 3 the incidence of excitatory phenomena is shown to be related to dose, this being plotted on a logarithmic scale. Except in the case of thiobarbiturates after opiate premedication there is a high degree of correlation between these factors, which is most marked with the methylated compounds. At all dose levels opiate premedication reduces the incidence of excitatory phenomena; likewise, methyl barbiturates cause a higher frequency than equivalent doses of thiobarbiturates.

Figure 4 shows the same analysis applied to the incidence of respiratory upset. Here again there is a good correlation between the frequency of this complication and dosage, but the differences between the effects of the two groups of intravenous drugs are less marked. Opiate premedication appears to offer no protection against the occurrence of cough, hiccup or laryngospasm.

The clinical significance of these findings is further illustrated in table III which shows the

<table>
<thead>
<tr>
<th>Dose mg/kg (equivalent to thiopentone)</th>
<th>Thiobarbiturates</th>
<th>Methylated barbiturates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atropine</td>
<td>Opiate-atropine</td>
</tr>
<tr>
<td>3-</td>
<td>91</td>
<td>81</td>
</tr>
<tr>
<td>4-</td>
<td>73</td>
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<td>54</td>
<td>76</td>
</tr>
<tr>
<td>8-</td>
<td>66</td>
<td>63</td>
</tr>
</tbody>
</table>

TABLE III

Incidence of uneventful (grade I) induction related to dosage.

![Graphs](image-url)

**FIG. 3**

Incidence of excitatory phenomena related to dosage of drugs (plotted on a logarithmic scale). ○ thiobarbiturates. x methylated barbiturates.
Incidence of respiratory upset related to dosage of drugs (plotted on a logarithmic scale).
- o thiobarbiturates.  
- x methylated barbiturates.

Incidence of completely uneventful inductions related to the dosage of drug used.

DISCUSSION
It must be pointed out that this was not a planned clinical investigation carried out under strictly controlled conditions, but rather a retrospective analysis of the data collected by a large number of anaesthetists with widely differing clinical experience. For this reason no statistical tests have been applied to the findings, but in spite of these limitations it has been possible to demonstrate clearly a dose/comlications relationship which is of great pharmacological interest and which is not without clinical significance.

It is generally agreed that with the inhalation anaesthetics “the depth of general anaesthesia varies directly with the partial pressure (tension) of anaesthetic agent in the brain” (Wollman and Dripps, 1965). Clearly this statement does not apply unreservedly to the intravenous barbiturates in current use, particularly if the depth of anaesthesia is assessed on a purely clinical basis. Many of the patients in this study, although deeply unconscious after large doses of drugs, could not have been considered to be in deep surgical anaesthesia.

In terms of cortical responsiveness the action of deepening barbiturate anaesthesia is usually considered to follow a biphasic pattern. The well-known release from inhibition in lightest levels of anaesthesia, accompanied by an increased sensitivity to somatic pain, results in patients “over-responding” to surgical stimuli, but this phenomenon disappears with increasing dosage of the drug and cortical responsiveness declines. The occurrence of excitatory phenomena with still increasing dosage probably does not represent a true triphasic effect, for the events observed during very light anaesthesia only occur in response to stimuli, while excitatory phenomena appear to occur spontaneously. However, in studies with antanalgesic premedication and a constant dose of intravenous drug, Dundee (1965) postulated that the term “spontaneous” may not be quite accurate with respect to excitatory phenomena, as this could represent an exaggerated response to the pain of the needle-prick or of other similar stimuli. On this basis the “triphasic” theory of action cannot be dismissed completely.

Slight structural changes may convert a hypnotic barbiturate into a convulsant. Cope and Hancock (1939) and Knoefel (1945) found that sulphuration frequently produced this effect although Richards (1951) noted that this has not been confirmed in man. Dundee, Barron and King (1960) and Barron and Dundee (1961) demonstrated conclusively that an alkyl (CH₃) group in the 1 position of the barbiturate nucleus endowed the drug with convulsant properties. It is generally agreed that this latter is of greater clinical significance than any effect that the addition of a sulphur atom may have. It would appear that in some circumstances the same drug may possess both stimulant and hypnotic properties depending on dosage. The stimulant action appears with increasing frequency with larger doses and its intensity is greater with methylated compounds. Unfortunately, it is not possible to undertake a similar
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...study with the available barbiturates, i.e. non-methylated non-sulphured compounds. Such an investigation would show whether the barbiturate nucleus per se or the methyl or thio side chains are responsible for these complications.

No similar explanation can be offered for the greater incidence of respiratory upset with higher doses of intravenous barbiturates. Extensive controlled studies by Dundee (1962, 1963) have failed to correlate the frequent occurrence of this complication with any particular side chain. Cough and hiccup occur much more frequently with buthalitone and methohexitone than with any of the other drugs in this study, and with these their relationship to dosage is more clearly demonstrated than with the others. These complications also differ from excitatory phenomena in that their occurrence is not lessened by opiate premedication. However, their reduction by parasympatholytic premedicants (Dundee and Moore, 1961; Dundee, 1965) supports the hypothesis of Burstein and Rovenstine (1938) that thiopentone and similar drugs stimulate the vagus, causing a general increase in sensitivity of respiratory reflexes during anaesthesia. This parasympathomimetic action may also be dose-related.

In unpublished studies Barron has related the frequency of hiccup with methohexitone to the rate of injection. This latter factor was not controlled in this present study and there may well have been a tendency for the more rapid injection of larger doses, but it is impossible to assess the significance of this on the present findings.

In view of the widespread use of intravenous anaesthetics, it may seem surprising that the relationship of two troublesome complications to the induction dose of barbiturate has not received more mention in the anaesthetic literature. However, most anaesthetists prefer thiopentone, thiamylal or thialbarbitone for routine hospitalized cases, usually following an opiate/antisialogogue premedication and these are the circumstances when they are least troublesome. Furthermore, it is not common practice to use doses of any of these drugs in excess of the equivalent of 6–8 mg/kg thiopentone. Methohexitone, the most popular methylated barbiturate, is frequently employed for minor procedures, particularly in out-patients, and the dose is restricted to below that likely to cause a high incidence of either excitatory phenomena or respiratory upset. Nevertheless, this dose/complication relationship is an important factor to be kept in mind in clinical trials of new drugs. Ignorance of its occurrence could explain some of the widely contradictory findings in the early studies of thiopentone and similar drugs.

This is only one of the many investigations which emphasizes the unreliability of barbiturate dosage, or blood or brain barbiturate content, as a guide to the depth of anaesthesia. Although an orderly pattern of changes in the electroencephalogram occurs correlated to depth of anaesthesia, Brand and his colleagues (1961) were unable to relate these to blood levels of thiopentone in different subjects. Even in the same subject, studies of “acute tolerance” to barbiturates have shown the blood level to be a poor index of the depth of anaesthesia. In man, Brodie and colleagues (1950) and Dundee, Price and Dripps (1956) demonstrated that the plasma concentration of thiopentone at the time of awakening depended on the dose administered; larger doses were associated with higher concentrations of the drug in the plasma at the return of consciousness.

Maynert and Klingman (1960) showed that this applied to dogs and that the causal relationship between dosage and depth of anaesthesia was related to either peak concentration of the drug attained in the central nervous system or the maximum intensity of depression caused by the drug. All these factors combined to reveal our ignorance as to the basic mechanism involved in barbiturate anaesthesia.

REFERENCES


