THE INTERACTION OF SUXAMETHONIUM WITH PROPANIDID AND THIOPENTONE

BY

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SUMMARY

An investigation was carried out in adults aged 20–60 years comparing the interaction of propanidid or thiopentone with the muscle relaxant suxamethonium. An attempt was made to correlate the apnoea time with the incidence and severity of muscle pains. No correlation was found between the apnoea times and the incidence of muscle pains. The overall incidence of muscle pains was 19 per cent. The older age-groups of both sexes had a significantly shorter apnoea time with propanidid than with thiopentone, when the drugs were used in combination with suxamethonium; this was also true of the young females. On the other hand, there was no difference in the young males between propanidid and thiopentone and their interaction with suxamethonium, but young men had a higher incidence of muscle pains than anybody else.

Several reports have indicated that propanidid prolongs the duration of apnoea following injection of suxamethonium (Howells et al., 1964; Clarke, Dundee and Daw, 1964; Clarke, Dundee and Hamilton, 1967; Doenicke et al., 1968). No reports have been seen concerning the effect of propanidid on muscle pain after suxamethonium. The incidence of muscle pain following the use of thiopentone and suxamethonium has varied widely according to published reports (Churchill-Davidson, 1954; Foster, 1960; Newnam and Loudon, 1966).

A study was undertaken to compare the interaction of propanidid or thiopentone with suxamethonium and to determine whether the duration of apnoea was related to the incidence of muscle pains or fasciculation.

METHODS

A double-blind trial could not be undertaken because of the dissimilarity of the two induction agents. Patients were allocated to one of two groups, the allocation being made according to the last digit of their case number. Propanidid was given to the patients whose case-number final digit was even and thiopentone to those in which it was odd. The trial was designed on a latin square basis such that there were approximately even numbers of patients of either sex in each group, and to a lesser extent similar numbers of patients over the age of 40 were evenly divided between the two groups (see table I). Propanidid and thiopentone were each used in 2.5 per cent solutions, as it was felt that a more uniform rate of injection could thus be achieved. Furthermore Clarke, Dundee and Hamilton (1967) stated that propanidid 2.5 per cent is equipotent with thiopentone 2.5 per cent.

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 40</td>
<td>21</td>
<td>13</td>
<td>34</td>
</tr>
<tr>
<td>Over 40</td>
<td>22</td>
<td>28</td>
<td>50</td>
</tr>
<tr>
<td>Total</td>
<td>43</td>
<td>41</td>
<td>84</td>
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The dosage in all cases was 250 mg of either induction agent. This injection, given over a period of 6–10 seconds through a No. 1 needle, was immediately followed by suxamethonium 50 mg which had been stored in a refrigerator until its time of use.

The duration of apnoea was noted following the injection of the suxamethonium. This was measured from the onset of apnoea to the onset of respiratory efforts (Clarke, Dundee and Daw, 1964; Doenicke et al., 1968).
The timing of the apnoea was done with the aid of a stopwatch and performed double-blind by an independent observer who did not know what drugs were being used, or indeed the purpose of the timing. During the period of apnoea the lungs were inflated with a nitrous oxide and oxygen mixture, care being taken not to overventilate. No supplementary anaesthetic agents were administered during the period of apnoea but as soon as respiratory efforts were noted halothane was added to the gas mixture, and the lungs ventilated with this combination until stable anaesthesia was established. Throughout the operative procedure the patient spontaneously breathed the anaesthetic mixture through a Magill circuit (Type A; Mapleson, 1954). All anaesthetics were administered by the same person. The operations were all completed by 4.30 p.m. but patients were not allowed out of bed until the next morning. Each patient was interviewed during the latter part of the morning of the first postoperative day and was asked in general terms how he felt. A patient who did not complain of pain was then asked the direct question, "Have you any aches or pains apart from in the wound site?" If the response was in the affirmative then the severity of pain was assessed. In patients who spontaneously complained the pain was also assessed according to whether it was moderate or severe. Pain was classified as severe, moderate or absent. If the pain was such as to add materially to the patient's discomfort then it was classed as severe. All other aches or pains were classed as moderate.

Eighty-four patients (43 females) aged between 20 and 60 were included in the series. The types of operation for which they were anaesthetized were such that the duration did not exceed 30 minutes, and were of such a nature as to allow the patient to be up and out of bed the next morning; for example, carotid angiography and inguinal hernia. The patients received no premedication.

RESULTS

Respiratory effects.

Considering all patients the duration of apnoea produced by suxamethonium following induction with propanidid was, in general, briefer than that produced by suxamethonium following induction with thiopentone (fig. 1a). The average apnoea time following propanidid and suxamethonium was less than 2 minutes compared with an average time of 3 minutes following thiopentone and suxamethonium. This difference is statistically significant (P<0.0025).

Age and sex groups.

The frequency response curve of the apnoea times of males and females, receiving the combination of propanidid and suxamethonium showed a different pattern from that of patients receiving thiopentone and suxamethonium (figs. 1b, 1c).

In patients over 40 years who received propanidid and suxamethonium there was a significantly shorter period of apnoea than there was in those who received thiopentone and suxamethonium (P<0.005) (figs. 3a, 3b, 3c). This difference was also noted in females under 40 years (fig. 2c). The frequency curve of the duration of apnoea in young males (fig. 2b) was similar whether they received propanidid or thiopentone, in marked contrast to the curves in all the other age or sex groups. The difference in the response of the young males from that of all other series is significant at the 10 per cent level ($\chi^2=4.5841$; d.f. 3). This is a comparison of the sum of the curves of figure 2b with the propanidid frequency response curve of figure 1a.

Muscle pains.

The overall incidence of muscle pains was 19 per cent. The incidence was 11 per cent in males and 8 per cent in females. The Latin square design of this study enables the effects of a number of possible contributing factors to be isolated: namely, the age of the patient; the sex of the patient; the induction drug; the duration of apnoea; or combinations of two or more of these factors.

Age. There were 50 patients in the older age group of whom 7 had muscle pain, whereas 9 of the 34 younger patients had muscle pain. This difference is not statistically significant ($\chi^2=2.84; P>0.1$).

Sex groups. Seven of 43 females and 9 of 41 males experienced muscle pains. This difference is not statistically significant ($\chi^2=0.015; P>0.9$).
Duration of apnoea after the administration of suxamethonium 50 mg. The upper graphs show the response when thiopentone or propanidid was used as the induction drug. The middle and lower graphs show the apnoea frequency curves according to the patients' ages and sexes. It will be seen that the apnoea frequency curve after thiopentone or propanidid in the young males (2b) has a different pattern from all the others.

Effect of the induction drug.
Forty-two patients received propanidid, of whom 9 experienced muscle pains, compared with 7 of 42 patients who received thiopentone. The difference is not statistically significant ($\chi^2 = 0.30; P > 0.5$).

Apnoea time. Of the 42 patients in whom apnoea lasted less than 2 minutes 6 experienced muscle pains, whereas of the 42 patients in whom apnoea lasted more than 2 minutes 10 experienced muscle pain. The difference is not significant ($\chi^2 = 1.235; P > 0.2$).

If there was an association between the occurrence of muscle pain and duration of apnoea then the incidence of muscle pain would have increased among patients with longer periods of apnoea and this increase would have been greater as the apnoea time progressed.

The durations of apnoea are, considering the subgroups, arranged in 1-minute periods of
apnoea and the distribution of the apnoea times of each 1-minute period also showed no statistically abnormal distribution ($\chi^2 = 2.998$; d.f. 4; $P > 0.2$) (see fig. 4).

No correlation was found between any individual factor and the incidence of muscle pains. However, when combinations of factors are examined the frequency of muscle pains was found to be twice as high in the young males (5 out of 13) as it was for the older males (4 out of 28) and in fact was appreciably higher than for the rest of the population (11 out of 71). The difference in response of young men compared with all other patients was significant at the 10 per cent level ($\chi^2 = 2.417$; $P < 0.1$).

It is thus of interest that just as the apnoea time response for young males differed from the rest of the population tested so also did the incidence of muscle pains, even if it did not reach the customary levels of statistical significance. This failure to reach customary levels was due in part to the rather small numbers of this particular subset of the population studied.

**Fasciculations.**

No relationship was found between the severity or the incidence of fasciculations and the apnoea times. The incidence of muscle pains was unrelated to the incidence or severity of the fasciculations, neither were the fasciculations influenced by the induction agent, the age or the sex of the patient.

**DISCUSSION**

The results show that a 250 mg dose of propanidid 2.5 per cent, when compared with an equipotent dose, namely 250 mg, of thiopentone 2.5 per cent, does not potentiate the respiratory effects of suxamethonium 50 mg. Moreover, in the patients over 40 years the length of apnoea following induction of anaesthesia with propanidid and suxamethonium was significantly shorter than that following thiopentone and suxamethonium 50 mg. These findings may in part be explained by the fact that in this study a 2.5 per cent solution of propanidid was used throughout, for Ellis (1967), working with the rat phrenic nerve-diaphragm preparation, has stated that the myoneural block produced by propanidid and suxamethonium was in proportion to the dose of propanidid.

The reports of the incidence of muscle pains following the use of suxamethonium vary widely. This may well be in part related to the time interval between injection of the induction drug and suxamethonium. Craig (1964) emphasized this point and in his study of female patients the incidence of muscle pains was only 14 per cent when suxamethonium was given immediately after thiopentone. This compares with 16 per cent in the females in this series. It must be concluded that if, as Craig suggests, thiopentone offers considerable protection against muscle pains, then so does propanidid.

Doenicke and associates (1968) showed that rapid injection of propanidid results in a higher blood concentration of propanidid and that the drug is also more rapidly broken down in the serum following rapid injection. A dose of 250 mg of 2.5 per cent propanidid can be rapidly injected and it might be expected that the higher serum levels so produced would be able to afford an equal degree of protection against muscle pains as does thiopentone when the induction agent is rapidly followed by the relaxant. Of the patients in this series who experienced muscle pains, only two were severe. The rest only experienced moderate degrees of pain. It was not possible to
correlate the evidence of muscle pains with the duration of apnoea nor the incidence or severity of fasciculations.

There is no obvious reason why the young men should differ from the older patients in the response to suxamethonium and muscle pain, though Crawford (1969) has suggested that protein binding capacity is related to the level of sex hormones. If suxamethonium is transported in the body by plasma proteins, as may be expected in view of its ionization charges, this may be the explanation of the observed differences.

ACKNOWLEDGEMENTS

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REFERENCES


INTERACTION DU SUXAMETHONIUM AVEC PROPANIDID ET THIOPENTONE

SOMMAIRE

Une étude a été faite chez des adultes de 20-60 ans, comparant l'interaction de propanidid et thiopentone avec le myorelaxant suxamethonium. On a essayé d'établir le rapport entre l'incidence et la sévérité des douleurs musculaires. L'incidence générale des douleurs musculaires fut 19 pour cent. Les patients plus âgés des deux sexes présentèrent une apnée significativement plus courte avec propanidid qu'avec thiopentone, lorsque les médicaments étaient administrés en association au suxamethonium; il en fut de même chez les femmes. Mais il n'y eut pas de différence entre propanidid et thiopentone dans leur interaction avec suxamethonium chez les jeunes sujets de sexe masculin, mais ceux-ci manifestèrent plus de douleurs musculaires que tous les autres patients.

DIE WECHSELWIRKUNG VON SUXAMETHONIUM MIT PROPANIDID UND THIOPENTON

ZUSAMMENFASSUNG