THE PROTECTIVE EFFECT OF THIOPENTONE AGAINST MUSCULAR
PAIN AND STIFFNESS WHICH FOLLOWS THE USE OF
SUXAMETHONIUM CHLORIDE

BY
HENRY J. L. CRAIG
Lurgan and Portadown Hospital, Lurgan, Northern Ireland

SUMMARY

Some factors known to influence the incidence of muscle pain following suxamethonium chloride are the age and sex of the patient, the nature of operation and the time of ambulation. The protective effect of thiopentone against this after-pain was demonstrated in a controlled series of patients undergoing a standard minor operation. With a 5-minute interval between administration of thiopentone and suxamethonium 41 per cent developed after-pain; this fell to 14 per cent when there was no interval. This effect could not be demonstrated following induction with nitrous oxide and oxygen, which was followed by a higher overall incidence (55 per cent). It was concluded that the protective effect of thiopentone was of short duration, but that some protective effect remained even after 5 minutes.

Muscle pain and stiffness following the use of suxamethonium was first mentioned as a possible drawback to the use of the drug by Bourne, Collier and Somers (1952), and a year later Currie (1953) noted the occurrence of subcostal pain following its use, although he attributed this to the use of intermittent positive pressure respiration. Sanger (1953) correctly related this type of pain to the use of short-acting depolarizing relaxants. In the following year Churchill-Davidson (1954) published results showing a high incidence of muscle pain and stiffness in out-patients undergoing minor operative procedures in which suxamethonium was used as part of the anaesthetic technique. He also showed that a much lower incidence occurred in in-patients undergoing similar procedures but who were kept in bed for 48 hours following operation.

Since this time about a score of papers have confirmed that these aches and pains are the result of the use of this type of drug and that they constitute a real drawback to the use of suxamethonium, especially in patients ambulant early after operation.

From a perusal of these papers the following facts emerge:

(1) The muscular pain and stiffness is like that which occurs following violent and prolonged exercise of unaccustomed muscles (Leatherdale, Mayhew and Hayton-Williams, 1959; White, 1962).

(2) The commonest sites are the neck, shoulders, anterior chest wall, over the lower ribs and upper abdomen, usually in that order (Burtles and Tunstall, 1961; White, 1962). Other sites are the jaw (Bryson and Ormston, 1962) and the region of the upper and lower dorsal spine (Parbrook and Pierce, 1960). Some investigators claim that they are quite common in the limbs, but others found no limb pains due to suxamethonium (Burtles and Tunstall, 1961). Bryson and Ormston (1962) frequently found limb pains on the second postoperative day following Caesarean section in which intermittent suxamethonium was used. Severe pain may occur at a single site and mimic a serious condition, e.g. pleurisy or meningitis (Price, 1954; Burtles and Tunstall, 1961).

(3) The pains are less common in children, especially under the age of 9 years (Bush and Roth, 1961), and also in the older age groups, i.e. over 50 or 60 (Foster, 1960; Burtles and Tunstall, 1961; Burtles, 1961). There is probably no real difference in incidence corresponding with age in the range of adolescence to 50 years (Leatherdale, Mayhew and Hayton-Williams, 1959).
(4) The sooner the patient is ambulant after operation the more likely is the occurrence of pain (Churchill-Davidson, 1954; Morris and Dunn, 1957; Burtles and Tunstall, 1961; White, 1962).

(5) A higher incidence in females than in males is found by most investigators, the ratio being about 2:1 (Leatherdale, Mayhew and Hayton-Williams, 1959; Parbrook and Pierce, 1960). Leatherdale, Mayhew and Hayton-Williams suggested that this occurs because females normally take less physical exercise than men, but that women will take some exercise soon after discharge from hospital and are, therefore, more likely to be sufficiently exercising their muscles to notice symptoms, whereas men are likely to be resting during this period. This, however, would hardly explain the findings of Bush and Roth (1961) who noted an incidence in girls twice as high as in boys, both groups being in the age range of 5 to 14 years. Foster (1960) did not find this difference between the sexes, and his figures actually show a higher incidence in men, but, as he admits, factors such as age, site of operation and time of ambulation were not controlled in this series and the two sex groups may not be evenly matched in these respects.

(6) According to most authors there seems to be no definite relationship between physical fitness, muscle development and power or body type and the incidence or severity of these pains (Leatherdale, Mayhew and Hayton-Williams, 1959; Morris and Dunn, 1957), although only a few have investigated this aspect. Halldin and Palmer (1961) claim to have found a tendency to an increased incidence in patients with less well developed or exercised muscles, but their figures are not conclusive.

(7) The nature of the operation may indirectly affect the issue by determining the length of time a patient is confined to bed, and postoperative wound pain may mask the pain and stiffness due to suxamethonium either by distracting the patient's attention or by being superimposed on the same site. Endotracheal intubation may, in itself, be responsible for subsequent pain and stiffness in the neck. Burtles and Tunstall (1961) found that two out of fifteen patients had neck pain and stiffness following intubation with non-depo-
apart from the prior use of non-depolarizing relaxants in small doses (Morris and Dunn, 1957; White, 1962) no drug or combination of drugs has been found which consistently reduces the occurrence of pain, and so far no successful treatment of established pain has emerged. The reported incidence of pain following the use of suxamethonium varies widely between 14 per cent (Churchill-Davidson, 1954) and 89 per cent (Mayrhofer, 1959).

These variable findings make difficult the assessment of the efficacy of any drug or method of anaesthesia as a means of preventing pain and stiffness following the use of a depolarizing relaxant. The main reason for this variation in results would appear to be insufficient standardization of the many factors known to influence the incidence of this type of pain. These include the age and sex of the patient, the method of anaesthesia, the type of operation, the time of ambulation, and the time and method of questioning the patient. Not only does lack of standardization of these factors invalidate comparison of one author's series with another but it also renders doubtful the findings of investigators who have failed to take into consideration some or all of these factors. Sometimes, for instance, entirely unselected groups of patients undergoing a wide variety of operations using different anaesthetic agents and techniques are compared with similarly unselected groups and the frequency distribution of the above factors ignored entirely, or inadequately recorded at best. Many studies also lack adequate controls.

Burtles and Tunstall (1961) suggested that thiopentone had some protective effect against the aches and pains. Ruddell (1959) disagrees with this view. Burtles and Tunstall (1961) and also Burtles (1961) claim that the interval between injection of thiopentone and suxamethonium is important but in neither paper are there conclusive data to support this statement.

The purpose of the study reported here was to determine the influence, if any, of thiopentone on the incidence of muscle pain and stiffness following the use of suxamethonium chloride (Scoline) in a series of patients in which the factors already discussed were controlled as far as is possible in clinical practice. A control series was included to distinguish between pain resulting from the use of suxamethonium and that which was unrelated to the use of this drug.

**METHOD**

**Patients.**

A total of 430 female patients undergoing minor gynaecological operations were studied. All were in good physical condition and none of them was on any form of drug therapy prior to operation. Age ranged from 18 to 80 years, but the majority (94 per cent) were under 50 years. The patients were divided into five groups as follows:

- **Group 1.** These patients did not receive suxamethonium (100 patients).
- **Group 2.** Suxamethonium was given immediately after thiopentone induction (120 patients).
- **Group 3.** Suxamethonium was given 5 minutes after thiopentone induction (110 patients).
- **Group 4.** Suxamethonium was given immediately after a gaseous induction with nitrous oxide and oxygen (50 patients).
- **Group 5.** Suxamethonium was given 5 minutes after induction with nitrous oxide and oxygen (50 patients).

**Anaesthetic method.**

A standard premedication of pethidine 50–100 mg was given on the basis of body weight (under 51 kg, 50 mg; 51–76 kg, 75 mg; over 76 kg, 100 mg). Atropine 0.6 mg was also given. Anaesthesia was induced with thiopentone sodium 4.7 mg/kg, or with nitrous oxide 10 l/min, the facepiece being lowered gently on to the patient's face and oxygen added as soon as consciousness was lost. Anaesthesia was maintained with 75 per cent nitrous oxide in oxygen and 1¼–2 per cent halothane (Fluotec vaporizer) administered through the Magill semiclosed circuit of a Boyle machine using a total gas flow of 8 l/min.

A standard dose of 25 mg of suxamethonium was employed throughout, irrespective of the weight of the patient. When thiopentone was used the relaxant was given either immediately or after an interval of 5 minutes. When a gaseous induction was employed suxamethonium was given when consciousness was lost or 5 minutes after induction.
PROTECTIVE EFFECT OF THIOPENTONE AGAINST MUSCULAR PAIN

Table I

Showing site of muscle pain and/or stiffness and its percentage incidence in a control group of patients and in two groups receiving suxamethonium chloride 25 mg; (A) immediately, and (B) 5 minutes, after thiopentone 4.7 mg/kg.

<table>
<thead>
<tr>
<th>Site of pain and/or stiffness</th>
<th>Control group</th>
<th>Suxamethonium group A</th>
<th>Suxamethonium group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower abdomen</td>
<td>13</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Low back</td>
<td>11</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Limb</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Sore throat</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Jaw and neck</td>
<td>0</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>Shoulders and upper back</td>
<td>0</td>
<td>2.5</td>
<td>22</td>
</tr>
<tr>
<td>Pectoral and retrosternal</td>
<td>0</td>
<td>2.5</td>
<td>2</td>
</tr>
<tr>
<td>Costal margin and epigastric</td>
<td>2</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

Number of patients in each group 100 120 110

Observations.

The ages and weights of all patients were recorded. The duration of operations varied from 8 to 20 minutes. All patients were ambulant, to the bathroom at least, 10-17 hours after return from theatre. All were interviewed by the author 24-30 hours after operation and asked, "How are you feeling this morning?" If the patient was in bed she was asked, “Have you been up today?” and “How did you feel when you were up?” If, in reply, no mention was made of pain or stiffness leading questions were used: “Have you any aches or pains this morning?” When the answer was negative, the next question was, “Are you stiff or sore anywhere?” If a history of pain or stiffness was given at any stage the exact site or sites were determined.

Statistical method.

The results obtained from each group were compared using the chi-square ($\chi^2$) test. $\chi^2$ was calculated from the sum of the terms $\frac{(O - E)^2}{E}$ where O was the observed frequency of suxamethonium pain being present or absent. E was the calculated expected frequency assuming no difference existed between the groups being compared. As only two groups were compared at a time the degree of freedom was one. Using the value of $\chi^2$ obtained, the probability (P) of the difference between the two groups occurring purely by chance was read from distribution of $\chi^2$ statistical tables under the column of one degree of freedom. A value of P of less than 0.05 was taken to mean that a significant difference existed.

RESULTS

Table I shows the findings in 100 patients in the control series who received no suxamethonium, in 120 patients who were given a single 25-mg dose of suxamethonium immediately after induction with thiopentone (A), and in 110 patients given a single 25-mg dose of suxamethonium 5 minutes after thiopentone induction (B). Lower abdominal pain occurred in all groups but was more frequent in the control series. The incidence of low back pain was similar in all groups, and limb pains were absent apart from unilateral tenderness over intramuscular injection sites. Other regions in which pain occurred show a zero incidence in the control group, apart from the epigastric and costal margin area, but even here the incidence in the controls is only one-third of that found in patients who received suxamethonium.

Excluding lower abdominal, low back and limb pain from the results (table II) the control series showed an incidence of 2 per cent and the first suxamethonium series 14 per cent. This can be regarded as a significant difference both in a clinical and a statistical sense ($\chi^2=10.23$; P<0.01).

In the suxamethonium group no obvious difference in the incidence of pain and stiffness with reference to age can be seen in the 20-50
TABLE II  
Showing incidence of pain and/or stiffness of a suxamethonium type in control groups who had no suxamethonium and in a group having suxamethonium 25 mg immediately after thiopentone 4.7 mg/kg, each group being subdivided into 10-year age groups. Presence of pain or stiffness is indicated by "positive".

<table>
<thead>
<tr>
<th>Age group</th>
<th>Control (no suxamethonium)</th>
<th>Suxamethonium immediately after thiopentone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>% of total</td>
</tr>
<tr>
<td>10-yr.</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>20-yr.</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>30-yr.</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>40-yr.</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>50-yr.</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>60-yr.</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Totals</td>
<td>100</td>
<td>—</td>
</tr>
</tbody>
</table>

TABLE III  
Showing incidence of pain and/or stiffness of a suxamethonium type following suxamethonium 25 mg given either (1) 5 minutes or (2) immediately after induction of anaesthesia with thiopentone 4.7 mg/kg. Anaesthesia was maintained with nitrous oxide and oxygen supplemented by halothane 1.5-2 per cent. "Positive" indicates presence of pain or stiffness.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Interval between thiopentone and suxamethonium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 minutes</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
</tr>
<tr>
<td>10-yr.</td>
<td>3</td>
</tr>
<tr>
<td>20-yr.</td>
<td>33</td>
</tr>
<tr>
<td>30-yr.</td>
<td>39</td>
</tr>
<tr>
<td>40-yr.</td>
<td>27</td>
</tr>
<tr>
<td>50-yr.</td>
<td>7</td>
</tr>
<tr>
<td>60-yr.</td>
<td>1</td>
</tr>
<tr>
<td>Totals</td>
<td>110</td>
</tr>
</tbody>
</table>

year groups, the number of cases under 20 and over 50 being too small for any conclusion to be drawn.

Table III shows that 41 per cent of patients who were given 25 mg of suxamethonium 5 minutes after thiopentone subsequently had suxamethonium type muscle pain, as compared with 14 per cent of those to whom suxamethonium was given immediately following thiopentone. There is a highly significant and obvious clinical difference between the incidence of muscle pains in the groups who received suxamethonium at different times ($\chi^2 = 20.85; P<0.001$).

It can also be seen from table III that a higher incidence was recorded in the younger age range in the group in which there was an interval between injections of thiopentone and suxamethonium. Comparing the results in the 10-29 years age group with those in the 30-49 age group, a significant difference is found ($\chi^2 = 5.97; 0.05>P>0.01$). The difference in age distribution between the two groups is slightly biased toward the younger age group in the series in which there was no interval between the thiopentone induction and the giving of suxamethonium.
The effect of using a gaseous induction instead of thiopentone is shown in table IV. When suxamethonium 25 mg was given immediately after loss of consciousness the incidence of pain and stiffness of a suxamethonium type was 56 per cent as compared with 54 per cent when 5 minutes separated the induction and the giving of suxamethonium in the same dosage. In both these groups the incidence of pain was significantly higher than that observed in the group who received suxamethonium immediately after thiopentone ($\chi^2 = 31.14$ and $28.89$; $P<0.001$ in each case). A lower incidence (41 per cent) was found in the group who had suxamethonium 5 minutes after thiopentone (table III) compared with the 54 per cent in those who received suxamethonium 5 minutes after a nitrous oxide and oxygen induction (table IV), but the difference is not statistically significant ($\chi^2 = 2.38$; $0.1>P>0.05$). However, if both the inhalational induction groups are considered together (incidence 55 per cent) and compared with the thiopentone series (table III) a statistically significant difference was found ($\chi^2 = 4.16$; $P<0.05$).

**DISCUSSION**

In this type of study one series of patients should be compared with a similar series differing only in the factor under investigation. A large number of patients is required. To establish a control series a type of operation for which a relaxant is not essential should be selected. For these reasons a group of patients undergoing minor gynaecological procedures was chosen for this study. In these patients, who have minimal postoperative discomfort and no painful wounds, it is relatively easy to detect pain and stiffness due to factors other than the operative procedure. All are of the same sex, most lie in the age range 20 to 50 years, all occupy the same position on the operating table, and the duration of the operation is fairly standard. Furthermore, the same basic anaesthetic technique can be used in all cases and the time of ambulation can be made constant.

The purpose of having a control series was to deduce which pains could be attributed to suxamethonium and not to factors connected with the operation itself, such as the positioning of the patient on the operating table. Low back pain, which is a common sequel to many operations (Edmonds-Seal and Eve, 1962), occurred in both control and suxamethonium groups with no significant difference in frequency. Many of the cases who had postoperative backache had similar symptoms prior to operation. Lower abdominal pain was actually more frequent in the control group than in the suxamethonium groups. In all groups pain in the limbs was confined to the thigh and corresponded to the site of intramuscular injection of premedication. Therefore it was decided to omit these regions when counting the number of patients in whom pain and stiffness of a suxamethonium type occurred.
From the results of the two series in which thiopentone preceded the suxamethonium it can be seen that the timing of the injection of the depolarizing relaxant in relationship to the thiopentone is very important. The number of patients complaining of a suxamethonium type of pain was increased threefold when an interval of 5 minutes separated the administration of the two drugs.

It could be argued that thiopentone has some protective effect of short duration as far as this type of pain is concerned. Alternatively the state of general anaesthesia might produce some gradual change, increasing the likelihood of pain occurring, which could either be a specific effect of one or more of the inhalational drugs used or due to general anaesthesia itself. A third possibility is that thiopentone actually increases the incidence of muscle pain but the thiopentone-suxamethonium interval is too short in the first series for this effect to be fully seen.

In order to elucidate these points the two groups in which no thiopentone was used were studied. The results showed no significant difference in incidence of pain in relationship to the timing of the dose of suxamethonium, so it would appear that the administration of nitrous oxide, oxygen and halothane for 5 minutes prior to the giving of suxamethonium had no effect on the incidence of pain of a suxamethonium type. When patients were given suxamethonium immediately after induction of anaesthesia those in whom anaesthesia was induced with nitrous oxide developed the suxamethonium type of pain four times more frequently than those in whom anaesthesia was induced with thiopentone.

Comparing the two groups who received suxamethonium 5 minutes after induction a lower incidence of pain occurred in the thiopentone group, but the difference is not of statistical significance. However, if it is accepted that timing of the dose of suxamethonium is unimportant in the two series in which anaesthesia was induced with nitrous oxide and if these are considered as one group to be compared with the group to whom suxamethonium was given 5 minutes after induction with thiopentone then a significant difference is observed. This indicates that some residual protective effect still remains even 5 minutes after thiopentone has been given.

It can be concluded that thiopentone has a protective effect against the pain and stiffness caused by a single 25-mg dose of suxamethonium chloride and that this protection is of short duration, having very nearly disappeared after 5 minutes.

It would seem reasonable that if suxamethonium is to be used as part of an anaesthetic technique it should be given in a single dose and immediately after the thiopentone if pain and stiffness are to be minimized and that repeated doses of suxamethonium are more likely to cause postoperative discomfort as the thiopentone-relaxant interval will be increased.

ACKNOWLEDGMENTS

Thanks are due to Mr. T. J. M. Myles and Dr. W. F. K. Morrow, and other members of the hospital for their assistance and co-operation in this study, and to Dr. J. V. Deakin of Allen and Hanburys Limited, Medical Department, for assistance with bibliography.

Thanks are also due to Professor J. W. Dundee and Dr. C. A. G. Armstrong for their help and advice in the preparation of this paper.

REFERENCES


L'EFFET PROTECTEUR DE LA THIOPENTONE CONTRE LA DOULEUR MUSCULAIRE ET LA RAIDEUR QUI SUIT L'EMPLOI DU CHLORURE DE SUXAMETHONIUM

SOMMAIRE

Quelques facteurs connus pour influencer l'incidence des douleurs musculaires faisant suite au chlorure de suxaméthonium sont l'âge et le sexe du malade, la nature de l'opération et le moment de la marche. L'effet protecteur de la thiopentone contre cette douleur secondaire a été démontré dans une série de malades et de témoins subissant une minime opération standard. Pour un intervalle de cinq minutes entre l'administration de la thiopentone et du suxaméthonium, 41% ont présenté une douleur secondaire; ce chiffre est tombé à 14% quand il n'y avait pas d'intervalle. Cet effet n'a pas pu être démontré à la suite de l'induction par l'oxyde nitreux et l'oxygène, à laquelle a succédé une plus forte incidence totale (55%). On a conclu que l'effet protecteur de la thiopentone était de brève durée, mais qu'un certain effet protecteur persistait même après cinq minutes.

DIE SCHUTZWIRKUNG DES THIOPENTON GEGEN MUSKELSCHMERZEN UND STEIFHEIT ALS FOLGE DER ANWENDUNG VON SUXAMETHONIUM CHLORID

ZUSAMMENFASSUNG