AN APPRAISAL OF TACRINE-EXTENDED SUXAMETHONIUM

BY

A. R. HUNTER

SUMMARY

The use of tacrine-extended suxamethonium in 117 cases is described. The extent of the myoneural block was monitored with the aid of a nerve stimulator. In patients in whom an intubating dose of suxamethonium unaccompanied by tacrine produced a somewhat prolonged apnoea, there was a significant but relatively unimportant prolongation of the action of tacrine-extended suxamethonium. Dual block developed in some cases, notably in the group of patients undergoing gastric and gall bladder surgery, but was always transient. Its presence gave no indication whatever of the likelihood of the appearance of postoperative respiratory insufficiency. Inadequate respiration on withdrawing the anaesthetic was noted in thirteen patients. In seven this amounted only to a chin tug and did not involve disorganization of respiratory movements, but six patients needed periods of artificial ventilation. It is concluded that this is a safe and satisfactory technique, particularly for the sick patient. The development of dual block during the period of muscle paralysis was unimportant.

The extension of the action of suxamethonium by means of anticholinesterase drugs such as tacrine has been quite common practice for a number of years. The technique offers the advantages of producing a reasonable period of muscular relaxation without any great danger of blood pressure change (Hunter, 1965). There have been few critical assessments of the value of this technique since it was originally described in this country by Barrow and Smethurst (1963). Further, there has been a widespread suspicion that a dual block might develop after the repeated administration of suxamethonium and that this might lead to inconvenient delay in the return of normal breathing at the end of surgical operations. For this reason the technique has achieved little popularity.

No longer, however, need the development of dual block be a matter of surmise. There are available for routine use in the operating theatre a number of simple stimulators which will activate nerves through intact skin but whose electrical impulse is too short to cause a contraction of muscle fibre. With the aid of such a stimulator it is possible to determine both the extent and the nature of the paralysis in a patient to whom suxamethonium is being given (Brown, 1967, personal communication). For this reason it seemed worthwhile to examine the usefulness of tacrine-extended suxamethonium in some detail.

METHODS

Patients undergoing the procedures of general surgery were investigated. The actual operations performed are listed in table I together with their duration, the duration of the period of surgical relaxation required and the number of doses of tacrine and suxamethonium given.

Patients were premedicated with pethidine (25–75 mg) or morphine (10 mg) together with atropine (0.6 mg). Those with chronic bronchitis or asthma causing symptoms at the time of operation also received 25–50 mg promethazine. The very sick were premedicated with atropine 0.6 mg only.

Anaesthesia was induced with a sleep dose of thiopentone, usually about 0.25 g, and enough to abolish the eyelash reflex. This was followed by suxamethonium 5 mg per 6.35 kg (=1 stone) of (estimated) body weight. Thereafter an oral airway was inserted and the patient's lungs rhythmically inflated with oxygen for 30 seconds.

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Direct laryngoscopy was performed, and the nozzle of a Macintosh spray, loaded with 4 ml of 4 per cent lignocaine solution, was passed into the trachea and the contents of the spray blown out. Intubation with a cuffed tube was then performed and the patient connected to a Boyle apparatus through which nitrous oxide 6 l./min and oxygen 3 l./min were flowing. After intubation of the trachea the lungs were inflated as often and as deeply as was necessary to prevent cyanosis and to avoid, it was hoped, carbon dioxide retention. The time between the injection of the suxamethonium and the return of normal breathing was noted to the nearest minute. If breathing did not return within 7 minutes of intubation a Medelec stimulator was used to determine whether the apnoea was due to continuing myoneural block or to central depression of respiration. After normal breathing had returned anaesthesia was stabilized on nitrous oxide, oxygen and halothane 0.5—1 per cent.

When relaxation was required tacrine 15 mg, atropine 0.3 mg and suxamethonium 30 mg were injected intravenously, irrespective of body weight. The extent of the myoneural block and its nature was followed by applying the electrodes of the stimulator, firing at 3 impulses per second, to the side of the patient's head at a point about 2.5 cm above and behind the external angular process of the frontal bone. The result of stimulating at this point was visible contraction of the orbicularis oculi and the jaw muscles on that side. Dual block was considered to be present when, with the stimulator working at this rate, it was shown that the first contraction was more forcible than its successors. Because it was impossible to measure the actual force of contraction the more orthodox failure to sustain a tetanus could not be demonstrated. Post-tetanic facilitation was, however, sought. Dual block was not recorded in its absence. With the stimulator working at maximum intensity the visible contraction of the ocular muscles returned more quickly than that of the jaw muscles. It was possible also to form an estimate of the force of contraction of the jaw muscles. When they responded normally the myoneural block everywhere in the body had largely passed off. More relaxant was then given.

After the first 30-mg dose, suxamethonium was given in 10-mg doses except when the patient seemed to be developing tachyphylaxis to this drug, when doses of 20 mg were employed. Additional 15-mg doses of tacrine were given approximately every half-hour unless the end of the operation was immediately in sight. The indication for additional doses of tacrine was a fall in the duration of action of a single dose of suxamethonium to some 5—7 minutes.

The patients studied were all in-patients of Stepping Hill Hospital, Stockport. The cholinesterase determinations were performed in the biochemical laboratory of Manchester Royal Infirmary by the method of de la Huerga, Yesinick and Popper (1952).
RESULTS

In all 117 patients were studied. In contradistinction to the findings of Macdonald (1967) there was found to be a close correlation between the patient's response to stimulation and the profundity of the surgical relaxation.

The figures in table I confirm the original observations of Barrow and Smethurst (1963) that approximately 15 minutes relaxation may be expected from the first dose of suxamethonium of 30 mg and that two doses are likely to be required during the second 15 minutes. There is no striking difference between different operations as far as concerned the requirements for suxamethonium and tacrine (table I).

Abnormal responses: incidence.

Three types of abnormal response were noted. Prolongation of apnoea was noted in twenty-seven cases following the initial dose of suxamethonium. (An arbitrary upper limit of normal of 4 minutes was accepted for this purpose.)

Dual block with fade and post-tetanic facilitation was demonstrated in twenty-one patients.

Inadequate breathing at the end of operation was noted in thirteen patients; these were retained in the recovery ward adjacent to the theatre until breathing returned to normal.*

The distribution of these abnormal responses and the percentage incidence of these complications are shown in table II. From this table it will be seen that prolongation of the effect of the initial dose of suxamethonium had a more or less uniform incidence throughout all the cases of the group. Dual block was relatively infrequent in those undergoing genito-urinary and hernia surgery but commoner in those undergoing appendicectomy and operations in the upper abdomen or on the bowel. It may well be, however, that this greater incidence merely reflects the longer duration of these latter procedures, although this cannot be the whole explanation because dual block was never seen during any of the fifteen operations on the kidney and ureter but occurred in 35 per cent of the forty-three patients undergoing operations of comparable duration in the upper abdomen. This difference is of high statistical significance (P<0.001), as is the difference between the frequency of dual block in anaesthesia for upper abdominal operations and for bladder operations (P<0.001).

Prolonged action of initial dose of suxamethonium.

Twenty-seven patients showed this complication. In them the initial apnoea extended from 5 to 12 minutes with a mean of 7.1 minutes. As would be expected the first 30 mg of suxamethonium given with tacrine also had a somewhat longer effect in these patients, producing myoneural block, lasting 19.7 ± 4.9 minutes (table III). Even so, the longest period of paralysis produced by this dose of suxamethonium was 30 minutes and this is certainly not inconveniently long for any but the shortest of operations.

In ten of these patients cholinesterase levels were determined. The normal for the method is 130–310 units. The mean cholinesterase level in this group was 156 and the range 83–210 units. Although no cholinesterase figures were available for the remainder of the cases of this group the mean duration of apnoea in these ten cases was exactly the same as that in the group as a whole. There is every reason to accept them as a representative sample. Unfortunately facilities for determining dibucaine numbers were not available at the time at which this work was begun and it is impossible to decide which of these prolongations of the action of suxamethonium were due to disease and which were due to an inherited heterozygous abnormality of cholinesterase.

The duration of effect of second doses of suxamethonium was also apparently prolonged. After third doses it was also slightly longer but again the number of cases available is too small for assessment of statistical significance (table III).

Dual block.

In all twenty-one cases showed evidence of dual block. Nineteen of the records are available for further analysis but from table IV it will be seen that in eleven of these nineteen patients this
TABLE II
The frequency of complications after tacrine-extended suxamethonium. The figures marked with an asterisk differ significantly from that marked with a dagger. Other differences are not significant ($t = 3.77$ for the difference between “bladder” and “stomach and gall bladder” operations; $P < 0.001$).

<table>
<thead>
<tr>
<th>Complications</th>
<th>Site of operation</th>
<th>Total cases</th>
<th>Dual block</th>
<th>Initial prolonged apnoea</th>
<th>Delayed recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cases</td>
<td>% incidence</td>
<td>Cases</td>
</tr>
<tr>
<td>Kidney and ureter</td>
<td>15</td>
<td></td>
<td>-</td>
<td>0*</td>
<td>4</td>
</tr>
<tr>
<td>Bladder</td>
<td>26</td>
<td></td>
<td>1</td>
<td>3.8*</td>
<td>7</td>
</tr>
<tr>
<td>Hernia</td>
<td>8</td>
<td></td>
<td>2</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Appendix</td>
<td>9</td>
<td></td>
<td>-</td>
<td>0*</td>
<td>1</td>
</tr>
<tr>
<td>Stomach and gall bladder</td>
<td>43</td>
<td>15</td>
<td>35†</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>Bowel</td>
<td>16</td>
<td></td>
<td>3</td>
<td>17</td>
<td>5</td>
</tr>
</tbody>
</table>

TABLE III
The duration of action of suxamethonium extended by tacrine in normal and complicated cases. Means and standard deviations (for the 109 cases for which the necessary information was available). Figures in brackets indicate the numbers of cases in each group.

<table>
<thead>
<tr>
<th>Duration of paralysis produced by</th>
<th>Type of case</th>
<th>First dose of 30 mg suxamethonium (min)</th>
<th>Second dose of 10 mg suxamethonium (min)</th>
<th>Second dose of 20 mg suxamethonium (min)</th>
<th>Third dose of 10 mg suxamethonium (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal response</td>
<td></td>
<td>$14.7 ± 3.6$ (53)</td>
<td>$7.6 ± 2.1$ (29)</td>
<td>$9.3 ± 1.16$ (7)</td>
<td>$7.3 ± 2.3$ (21)</td>
</tr>
<tr>
<td>Prolongation of initial dose of suxamethonium</td>
<td></td>
<td>$19.7 ± 4.9$ (27)</td>
<td>$10.3 ± 5.1$ (12)</td>
<td>-</td>
<td>$8.3 ± 3.8$ (7)</td>
</tr>
<tr>
<td>Delayed recovery at end of operation</td>
<td></td>
<td>$19.9 ± 5.3$ (10)</td>
<td>$10.1 ± 3.4$ (9)</td>
<td>-</td>
<td>$6.8 ± 2.4$ (4)</td>
</tr>
<tr>
<td>Dual block</td>
<td></td>
<td>$14.7 ± 3.0$ (19)</td>
<td>$7.1 ± 1.7$ (14)</td>
<td>-</td>
<td>$6.5 ± 2.6$ (11)</td>
</tr>
</tbody>
</table>

TABLE IV
Dual block.

<table>
<thead>
<tr>
<th>(a) Duration of myoneural block until dual block apparent up to and including</th>
<th>No. of cases</th>
<th>15 min</th>
<th>30 min</th>
<th>45 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>(b) Doses of suxamethonium given before dual block appeared</td>
<td></td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
a suggestion that in those who had developed dual block a slightly larger repeat dose of suxamethonium (20 mg) was more often necessary than in the control groups but the numbers involved are too small to provide numerical proof of this point.

In table III are set out the durations of action of the first, second and third doses of suxamethonium. It will be seen that in these patients with dual block the duration of action of suxamethonium was substantially the same as it was in those with a normal response to the drug, and this in spite of the fact that six of the nineteen patients for whom this information is available developed dual block within a few minutes of the first dose of suxamethonium.

In no patient was dual block present in the orbicularis oculi muscles at the time of discontinuing the anaesthetic. In none of the patients who developed frank dual block was there any delay in restoring breathing, though one patient of the thirteen in whom there was some delay in restoring breathing, had shown some fade in the response of the jaw muscles only, but not in that of the orbicularis oculi, and was not included among the cases of dual block.

Delayed recovery of adequate spontaneous respiration.

This was noted in thirteen patients. In seven of them this simply involved a degree of chin tug which lasted for 5–10 minutes after the withdrawal of the anaesthetic. The tidal volume and respiratory minute volume were normal, and the phenomenon disappeared spontaneously without treatment in the course of the next 5–10 minutes. In the remaining six patients of this group however, periods of artificial ventilation varying from 15 to 55 minutes were required. The mean period was 27 minutes. This complication had a relatively high incidence in those undergoing surgery of the bowel (table II). It was also frequent in those who showed delayed recovery from the initial dose of suxamethonium. Further, the duration of the paralysis produced by the first 30-mg dose of suxamethonium with tacrine was 19.7 minutes in this group as compared with just under 15 minutes in normal patients. On the whole the patients in this group required more prolonged operations. This, however, was probably an incidental result of the disease states for which operation was being performed.

Finally, though all the patients in this group recovered immediately from their postoperative respiratory insufficiency, three of them died from other causes within 4 days of operation.

There was no evidence of dual block in any of these patients save in the one in whom fade was apparent in the jaw but not in the eye muscles. Some degree of myoneural block was present in three of them, but this consisted merely of a reduced response to stimulation and was of the typical depolarizing type. In the remaining ten the responses to stimulation of the nerves to the orbicularis oculi, and to the jaw muscles, were completely normal. There was no evidence of paralysis in other accessible muscles. Stimulation of the ulnar nerve at the wrist or behind the medial epicondyle and stimulation of the anterior femoral nerve as it passed under Poupart's ligament in five cases produced vigorous contractions of the muscle supplied by these nerves. There was, therefore, no suggestion that the response of the eye and jaw muscles was not typical of those elsewhere in the body.

The possibility that metabolic acidosis might have been responsible was considered. Four patients were given 100 m.equiv sodium bicarbonate intravenously. In none did any improvement result. In six patients, the plasma bicarbonate was determined, either before or after the administration of bicarbonate. Again there was no evidence of metabolic acidosis. (Total CO₂ 28–34 m.equiv/l. in the three given bicarbonate and 23–26 m.equiv/l. in those not so treated.)

DISCUSSION

This investigation has substantiated most of the previous claims concerning the usefulness of tacrine in extending the action of suxamethonium. The additional refinement of the use of a stimulator to demonstrate the presence of myoneural block completely removed the guesswork about the time when additional doses of relaxant were required. It is true that there is no antidote to paralysis by suxamethonium, but it is only very occasionally that an operation finishes unexpectedly and it was possible during this study to plan dosage of relaxant so that myoneural block had disappeared by the time the anaesthetic was discontinued. Where profound myoneural block was used for
the control of hiccough, during upper abdominal
surgery, the effect of the suxamethonium persisted
in one case. But this complication is also liable to
arise if large doses of other myoneural blocking
agents are used to control this disturbance.

The fact that 3 per cent of the population are
heterozygotes for the gene determining serum
cholinesterase has deterred many from using this
particular technique. It is very probable that
among the 117 patients investigated there should
have been two or more heterozygotes. In spite of
this no serious prolongations of the action of
suxamethonium were noted, and indeed in a
previous investigation of prolongation of the
action of suxamethonium the author found little
evidence of serious prolongation of the action of
this drug in heterozygotes (Hunter, 1966).

Further if the technique here described, in which
a single dose of suxamethonium without tacrine
is used for intubation, is employed, then those
with an abnormality of the cholinesterase likely to
cause serious prolongation of the action of the
drug will in fact be found before tacrine is given
and no harm will result. Such a patient, with this
abnormality, had an apnoea lasting 18 minutes
following suxamethonium 50 mg but his operation
was completed with the aid of a single small addi-
tional dose of the relaxant without the need to
give tacrine.

The fact that six patients of the series required
periods of artificial ventilation, varying from 15
to 55 minutes after the conclusion of the operation
cannot, however, be lightly dismissed. It is
intriguing that the majority of these cases were
apparently not suffering from myoneural block.

They did, however, fall within the original
description of the patient suffering from neostig-
mine-resistant curarization (Hunter, 1956) in that
they were all far from well and many of them had
advanced cardiovascular disease. Three of them
indeed proved how ill they were by dying in the
immediate postoperative period!

It is reasonable, therefore, to question whether
the relaxant was in any way responsible for the
postoperative respiratory insufficiency. Certainly
the experience of Campbell and colleagues (1967)
in Glasgow and Pollard (1969) would suggest that
some cases of so-called postoperative curarization
are in fact accounted for by respiratory insuf-
ficiency of cardiovascular origin and it would
certainly seem that some of those of the present
series were suffering from such a disability. The
high frequency of respiratory insufficiency in those
undergoing operations on the bowel is again
parallel with the early comments on neostigmine-
resistant curarization (Hunter, 1956). It was, how-
ever, a little disconcerting to find that the
administration of bicarbonate did so little to
improve them, and that when plasma bicarbonate
estimations were carried out metabolic acidosis
was conspicuous by its absence. This might well
have been expected (Brooks and Feldman, 1962)
either as a result of disturbance of bowel function
or because of peripheral circulatory insufficiency.

The most unexpected finding in this study
related to dual block. This phenomenon is re-
peatedly mentioned in the literature as a cause of
prolongation of the action of suxamethonium. It
was conspicuously absent from those in whom
adequate respiration was difficult to re-establish at
the end of operation. Both Sliom (1966) and
Older, Harris and Mitchard (1966) have, how-
ever, described cases in which dual block was
associated with a prolonged action of tacrine-
extended suxamethonium.

When dual block did appear during the opera-
tion it was an entirely transient phenomenon,
usually noted during mild to moderate paralysis,
i.e. when the response to stimulation of the
orbicularis oculi was visible, though not very
forceful, and the response to stimulation of the
lower jaw muscle had barely recovered at all. In
these patients it was also apparently unassociated
with any change in the duration of action of
suxamethonium, nor was there any completely
convincing evidence of resistance to the action of
the drug in those who had previously shown dual
block, though in fact the numbers of cases are
too small to allow any final conclusion on this to
be drawn. This accords with the findings of
White (1963) who showed that dual block, as
indicated by an increased sensitivity to gallamine,
could develop after relatively short periods of
administration of suxamethonium. The repeated
disappearance of dual block as the paralysis waned,
and in some cases its reappearance during re-
covery after paralysis by subsequent doses of
suxamethonium, served to emphasize its transient
nature. Indeed the findings of this investigation
indicated clearly that dual block is an incidental
 phenomenon in some patients at certain stages of paralysis by suxamethonium.

This conclusion would certainly seem to be supported by the observation of Macdonald (1967) that post-tetanic facilitation was very common in patients in whom tacrine was used to extend the action of suxamethonium. Smart (1964) reached a similar conclusion.

The discovery that dual block can appear quite early during paralysis by suxamethonium is likewise not new. It was made by White in 1963 and confirmed in Macdonald's series. This study has, however, indicated quite clearly—as indeed might well have been concluded from the previous work on the subject—that the presence of dual block is not necessarily associated with prolongation of the action of suxamethonium. This was Macdonald's experience (personal communication), and that of Katz and Ryan (1969) with suxamethonium alone. It would, therefore, seem that the fact that dual block may occasionally occur is not necessarily a contraindication to the use of tacrine to prolong the action of suxamethonium. On the other hand, instances of prolongation of the respiratory paralysis beyond the period of operation have been recorded by a number of observers (McCaul and Robinson, 1962; Barrow and Smethurst, 1963; Sliom, 1966; Older, Harris and Mitchard, 1966) and it remains to be shown whether the incidence of this particular complication, which the present study would suggest may in fact have little to do with myoneural block, is higher in patients to whom suxamethonium and tacrine is given than it is in those in whom any other relaxant is used.

REFERENCES


EXPERIMENTATION DE L'ASSOCIATION TACRINE-SUXAMETHONIUM

SOMMAIRE

L'auteur rapporte son expérience sur l'utilisation de l'association tacrine-suxamethonium chez 117 malades. L'étendue du bloc myoneural a été contrôlée à l'aide d'un stimulateur nerveux. Chez les patients sur qui une dose de suxamethonium non associée à du tacrine et administrée par intubation, produisit une apnée quelque peu prolongée, on a constaté une prolongation de l'action tacrine-suxamethonium relativement peu important mais significative. Un bloc de branche double est apparu dans deux cas notamment dans le groupe de patients subissant une intervention chirurgicale de l'estomac ou de la vésicule biliaire, mais ceci a toujours été transitoire. Toutefois sa présence ne donne aucune indication sur la probabilité d'apparition d'une insuffisance respiratoire post-opératoire. Chez 13 patients on a noté une respiration perturbée au retrait de l'anesthésique. Chez 7 ceci se traduisit seulement par un tirage et ne provoqua pas de troubles des mouvements respiratoires mais six d'entre eux nécessitèrent une ventilation assistée. L'auteur conclut qu'il s'agit d'une technique satisfaisante et sûre, en particulier chez les malades nauseux. L'apparition d'un bloc de branche double au cours de la période de paralysis musculaire est sans importance.

ÜBER DIE WIRKUNG VON SUXAMETHONIUM BEI VERWENDUNG MIT TACRINE

ZUSAMMENFASSUNG

Es werden die Ergebnisse der Anwendung von Suxamethonium in der Kombination mit Tacrine an 117 Patienten mitgeteilt. Das ausmaß des myoneuralen Blocks wurde mittels eines Nerven-Stimulators fort-

NORTHERN IRELAND ANAESTHETISTS GROUP

FORTHCOMING MEETINGS

MARCH 18, 1970
Address entitled: "Pneumatic Nonsense" by Professor J. S. Robinson, in the Wellington Park Hotel.

APRIL 22, 1970
Symposium on Intensive Care, in BMA House, 609 Ormeau Road, Belfast 7.

MAY 27, 1970
Annual General Meeting, in BMA House, 609 Ormeau Road, Belfast 7.

Meetings are held at 8 p.m.

Details from the Hon. Sec., Dr. G. W. Black, c/o Royal Belfast Hospital for Sick Children, Belfast BT12 6BE.