A clinical application of the property of anticholinesterase drugs to prolong the action of suxamethonium is described. A trial has been conducted using the anticholinesterase tetrahydroaminacrine (THA) in association with suxamethonium to provide muscle relaxation during 1,470 surgical operations. The technique involves the intermittent injection of small doses of suxamethonium (10 mg cation) following an initial priming dose of both THA and the muscle relaxant. The average consumption of suxamethonium is 75 mg cation per hour. The method facilitates the maintenance of an even degree of relaxation in response to intermittent injections of suxamethonium. Prolonged neuromuscular block is a hazard if the recommended scales of dosage be exceeded.

The cholinesterase inhibitors used in anaesthetic practice will, if administered concurrently with suxamethonium, potentiate and extend the duration of action of the latter drug. Over a period of three years the authors have conducted a series of clinical trials to determine the safety and efficiency with which various anticholinesterases can be used for this purpose during anaesthesia. The drugs were neostigmine, edrophonium, pyridostigmine and tetrahydroaminacrine, and preliminary trials indicated that of these, the last was the most suitable for further investigation (table I).

### Table I

<table>
<thead>
<tr>
<th>Anti-cholinesterase</th>
<th>Dose (mg)</th>
<th>Extension of apnoea (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>THA</td>
<td>10</td>
<td>12–15</td>
</tr>
<tr>
<td>THA</td>
<td>20</td>
<td>13–18</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>0.5</td>
<td>6</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>1</td>
<td>7–9</td>
</tr>
<tr>
<td>Edrophonium</td>
<td>5</td>
<td>4–4½</td>
</tr>
<tr>
<td>Edrophonium</td>
<td>10</td>
<td>5–6</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>0.5</td>
<td>4</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>1</td>
<td>4½</td>
</tr>
</tbody>
</table>

The “extension” effect of various anticholinesterases on patients whose response to suxamethonium 40 mg was a period of apnoea lasting approximately 3 minutes.

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TETRAHYDROAMINACRINE (THA)

THA is the hydrogenated form of the antiseptic aminacrine (fig. 1) and its experimental pharmacology has been extensively investigated in man and animals (Albert and Gledhill, 1945; Shaw and Bentley, 1949, 1953; Gershon and Shaw, 1958). It is a white crystalline water-soluble powder which is compatible in solution with pethidine, atropine and suxamethonium. It has no antiseptic properties (Albert et al., 1945) but in experimental and clinical use it shows marked anticholinesterase and decurarizing activity and is a non-specific stimulant to medullary centres. It produces in animals and man a rapid arousal from deep morphine narcosis. In clinical practice
it has been used to reverse paralysis induced by d-tubocurarine and gallamine, and also as a substitute for neostigmine in the treatment of myasthenia gravis (de la Lande, 1961, personal communication; McCaul, unpublished). The mode of elimination of THA is uncertain but the evidence points to early inactivation by redistribution, with subsequent detoxification in the liver. The relative potencies of THA and neostigmine are difficult to assess clinically but, as judged by decurarizing activity in man and animals, the ratio is approximately 30:1.

DESCRIPTION OF CLINICAL TRIALS

The method now described has been in use during the latter two years of the trial period. Techniques used during the first year have been discarded and will not be detailed, though observations then made will be discussed where appropriate. Pre-anaesthetic medication includes atropine in conventional doses and narcotics are added when indicated. Following the induction of anaesthesia by thiopentone and maintenance nitrous oxide and oxygen, a Mitchell or Gordh needle is inserted into a dorsal hand vein and through it, in adults, a mixed solution of THA 10 mg and suxamethonium 20 mg is injected.*

The period of paralysis which follows this initial injection is of 8 to 12 minutes duration (compared with 1 to 3 minutes after suxamethonium alone) and emergence is indicated by returning respiratory activity which is first noted as feeble diaphragmatic movement. A further injection of suxamethonium is then made, this time unaccompanied by THA, but the dose is reduced to 10 mg. Subsequent additional doses of suxamethonium 10 mg are given at each indication of waning paralysis (fig. 2). Towards the end of operation repeat doses of suxamethonium are frequently reduced to 5 mg or less when shorter periods of relaxation are required. The duration of neuromuscular block resulting from each successive dose of suxamethonium decreases progressively. Thirty to forty minutes after the initial injection a reduction of the duration of extension indicates the need for a supplementary injection of THA. These events are illustrated diagrammatically in figure 3.

*All doses of suxamethonium are expressed in cation weight.
Variations in technique.

On 640 occasions a test dose of suxamethonium 20 mg was administered several minutes prior to the first injection of THA and the response of the patient was noted. Some minutes later, when recovery from the test dose appeared to be complete, a mixed injection of THA and suxamethonium was administered as described above. In this way it was hoped that the patient would serve as his own control for each injection (fig. 4). The total number of patients anaesthetized in which these methods were used to provide muscle relaxation was 1,470 and the operations performed are listed in table II. The majority of patients were adults, but the technique was used in a small number of children undergoing intra-abdominal surgery or multiple dental extractions and the dose of THA was then estimated on a weight basis using Clarke's rule. The minimum age for the series was 4 years and the maximum 92.

RESULTS

There was no death attributable to the method. In all instances the duration of neuromuscular block was greater than would have been expected from suxamethonium alone. From a study of the cases submitted to a preliminary test dose of suxamethonium it became possible to predict the likely pattern of response to the combined injection (fig. 4).

Over 80 per cent of patients reacted to the test dose with a period of paralysis lasting approximately from 1 to 2 minutes, and to the combined dose by an extension of the period of paralysis to

<table>
<thead>
<tr>
<th>Operation</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal hysterectomy</td>
<td>358</td>
</tr>
<tr>
<td>Wertheim hysterectomy</td>
<td>11</td>
</tr>
<tr>
<td>Other major intra-abdominal surgery</td>
<td>407</td>
</tr>
<tr>
<td>Other major intra-abdominal gynaecological surgery</td>
<td>407</td>
</tr>
<tr>
<td>Intestinal surgery</td>
<td>83</td>
</tr>
<tr>
<td>Acute abdominal surgery</td>
<td>146</td>
</tr>
<tr>
<td>Gastrectomy</td>
<td>7</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>31</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>168</td>
</tr>
<tr>
<td>Forceps delivery</td>
<td>69</td>
</tr>
<tr>
<td>Dental extraction</td>
<td>17</td>
</tr>
<tr>
<td>Other operations</td>
<td>173</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1470</strong></td>
</tr>
</tbody>
</table>

Illustrating the extension in response of a patient who was given a preliminary injection of suxamethonium 20 mg alone.

Female, 70 kg.
Operation: abdominal hysterectomy.
Anaesthetic agents: thiopentone, nitrous oxide.
Total duration of relaxation, 60 min.
8 to 12 minutes. Thus, in most cases an extension of the expected duration of action of suxamethonium by a multiple of approximately 4 could be anticipated to result from the simultaneous administration of THA. This rule did not apply when the reaction to the test dose was extremely short or long. When the test dose response was 1 minute or less the average duration of extension was 7 minutes, and when the test response was over 5 minutes the extension period averaged 20 minutes. THA was not given to any patient whose test response to suxamethonium was longer than 10 minutes. There were two cases of grossly prolonged paralysis which were resistant to neostigmine. In both instances the paralysis followed the injection of the test quantity of suxamethonium and lasted approximately 1½ hours. Both patients were young healthy adults and, in the case in which it was possible to perform a pseudocholinesterase estimation, the level of free enzyme was reduced to 30 per cent of normal. Prolonged neuromuscular block of similar type did not occur in any patient in whom the administration of suxamethonium and THA was employed using the method described. However, in the pilot series when larger doses of suxamethonium were employed (40 to 50 mg of cation at each injection) a disturbing incidence of prolonged neuromuscular block occurred.

The onset of, and recovery from, paralysis was in all patients assessed clinically and, in addition, it was confirmed in approximately one-third of cases by the use of electrical stimulation of peripheral nerves (Mushin and Mapleson, 1957).

The first indication of return of muscular power was usually shallow respiratory movements, of the type often called "diaphragmatic flicker", which were transmitted through to the anaesthetic reservoir bag. Occasionally an increase of tension in the anaesthetic reservoir bag was the earliest indication of recovering muscle tone. Limb power returned slightly in advance of respiratory movement and, in the case of orthopedic operations, increasing muscle tone or even movement of the limb was sometimes the earliest indication of recovery from paralysis. The rate of recovery is slower than when suxamethonium is employed alone and it occurs over a period of 2 or 3 minutes. Thus there is ample warning of the necessity for repeat injections of the muscle relaxant drug. In the group of patients submitted to a preliminary test dose of suxamethonium, additional confirmation of the degree and duration of paralysis was obtained by electrical stimulation of peripheral nerves.

**Rate of use of suxamethonium.**

On analysis of the records of sixty consecutive abdominal operations the rates of consumption of suxamethonium and THA were found to average 1.4 mg/min and 0.3 mg/min respectively. This was in agreement with the observed consumption of suxamethonium administered by micro-drip to a group of patients undergoing surgery who had received a preliminary injection of THA.

**Side Effects.**

A theoretical objection to the simultaneous use of an anticholinesterase with suxamethonium, a drug having known cholinergic effects, is the possibility of accentuated muscarinic reactions such as bradycardia, sweating and salivation.

**Bradycardia.**

During the preliminary trials hyoscine was used as an alternative to atropine as a pre-anaesthetic drug. The dose of suxamethonium used was 40 mg cation and the dose of THA varied from 10 to 20 mg. The majority of patients in this group showed bradycardia of moderate to marked degree and pulse rates varying between 50 and 65 b.p.m. were usual. When bradycardia, even of severe degree, was present there was no occasion any other clinical indication of deterioration in the patient's condition. In the series now reported severe bradycardia was not a feature, though pulse rates were always lower than those recorded pre-operatively (fig. 5). Atropine was used freely if the pulse rate dropped to 60 b.p.m. and it invariably reversed the tendency to slowing. It is of interest that in animals bradycardia following the intravenous injection of large doses of THA can be prevented by preliminary administration of atropine or by vagal section and is therefore probably due to stimulation of the vagal centre (Shaw and Herman, 1959, personal communication). There was evidence in the pilot series that cardiac slowing was also related to the amount of suxamethonium used and to the speed of injection. Because of these considerations, and the additional liability of prolonged neuromuscular paralysis with large doses, the present maximum repeat dose of suxamethonium 10 mg was evolved and
sweating was frequently observed during the more traumatic stages of surgery and could always be abolished either by pulmonary hyperventilation or by the introduction of a volatile or non-volatile analgesic supplement. The drugs used for this purpose were pethidine, alphaprodine, cyclopropane, ether and halothane. In some cases sweating may have been the result of a rising Pco₂ as hyperventilation was deliberately avoided, it being felt that it might mask the onset of respiratory movements.

**Vomiting.**

Retching during the recovery phase occurred in 22 per cent of patients, and ceased with full return of consciousness. The incidence of delayed postoperative vomiting, which was being studied as a separate project, did not alter during the period of the trial when it was under investigation.

**Salivation.**

Apart from its occurrence during the period of retching excessive salivation was not noted.

**Intestinal motility.**

Intestinal motility was increased, the bowel was slightly contracted, and packing of abdominal contents were facilitated.

**Arousal from anaesthesia.**

Recovery of consciousness occurred within 3 to 4 minutes of the withdrawal of the anaesthetic gases. The rapidity of recovery from anaesthesia was uninfluenced by the use of analgesic drugs administered pre-operatively or in the course of operation. This was an almost constant feature during the trials and prompted further investiga-
tions into the effects of THA on arousal mechanisms which will be published separately. It has now been demonstrated that THA is a powerful antagonist to morphine- and pethidine-induced narcosis, and has been successfully used in the treatment of morphine overdosage (Stone, Moon and Shaw, 1961; McCaul and Robinson, 1961, in preparation).

Use during labour.

The combination of THA and suxamethonium has been used freely during anaesthesia for Caesarean section and for instrumental vaginal delivery. No instance of unusual variation from the normal range of foetal response to anaesthesia and delivery was observed.

DISCUSSION

Potentiation and extension.

The degree of paralysis produced was that which is normal after full doses of suxamethonium. The unusual features were, firstly, that an amount of suxamethonium which would normally cause a fleeting period of incomplete neuromuscular block would always, if administered with the anticholinesterase, result in total paralysis.

Secondly, the period of paralysis was invariably of longer duration than could be expected to follow suxamethonium alone. There appeared to be, therefore, in addition to an extension of action, a potentiation of the neuromuscular blocking effects of suxamethonium by THA. When this investigation was commenced there was widespread interest in the development of continuous or serial suxamethonium infusions to meet the requirements for profound relaxation during emergency surgery on the distended abdomen. At the same time an increasing number of incidents of prolonged neuromuscular block attributed to excessive use of suxamethonium were being reported. Continuous infusion of suxamethonium, though theoretically ideal, was in practice cumbersome for the anaesthetist working without assistance. The method now reported evolved from an attempt to overcome these obstacles and to extend the use of the short-acting relaxants for major abdominal surgery. The technique has some disadvantages; for example it involves multiple injections and may therefore be considered tedious by some, and with suxamethonium, however used, the patient is subjected to the risk of muscle pains and to the other sequelae arising from the use of depolarizing agents. On the credit side it allows the anaesthetist to ensure the profound relaxation associated with suxamethonium throughout operation and closure, and recovery from paralysis occurs spontaneously.

If doses of the drugs are kept within the limits set out here, the neostigmine-resistant type of curarization does not appear to be a risk and muscarinic side effects can be avoided or reversed by the use of atropine.

The series reported suffers from a defect that over 90 per cent of the patients were female and therefore reassessment of the dosage scale for muscular males may be desirable. In view of their different physiological status and drug reactivity it is not considered that this technique should be applied to the neonate. As the mode of elimination of THA is probably by liver detoxification, its administration to patients suffering from gross liver failure is, in the light of present knowledge, contraindicated. It has, however, been used extensively in patients suffering from less severe forms of liver disease occurring in pregnancy and in biliary obstruction. Patients suffering from renal disease, anuria or electrolyte imbalance, have not been excluded from the trial.

The technique described has many similarities to that first reported by Arrowood and Kaplan (1955) and later by Foldes et al. (1960). Both groups of workers used hexafluorenium as an “extensor” agent for suxamethonium. Towards the end of this clinical trial a small supply of hexafluorenium was made available to us by Professor Foldes for purposes of comparison. On a limited number of observations, it was apparent that hexafluorenium differed from THA in having little or no muscarinic side effects and in its capacity to produce a longer (approximately double) extension of suxamethonium activity.

Another interesting point of contrast between these two “extensor” drugs is that while the incidence and degree of post-suxamethonium muscle fasciculation is unaltered in patients prepared a few minutes earlier by the administration of THA it can be avoided by the prior injection of hexafluorenium. Thus, while THA possessed many advantages in comparison with neostigmine, edrophonium and pyridostigmine it did not compare as favourably with hexafluorenium.
ACKNOWLEDGMENTS

Professor F. H. Shaw, Department of Pharmacology, University of Melbourne, provided much of the stimulus for this trial and has undertaken extra experimental work on our behalf. The surgical and obstetric staff of the Royal Women's Hospital, Melbourne, were generous in their co-operation.

The trial supplies of THA were provided jointly by Monsanto Chemicals of Australia and by Messrs. W. H. Woods Pty. Ltd. of Melbourne under the trade name "Tacrine".

Suxamethonium was supplied by Parke Davis & Co. Ltd (Scoline) and May and Baker Ltd. (Brevadil M).

REFERENCES


SUMMARY

Description d'une application clinique de la capacité des substances anti-cholinestérasiques de prolonger l'action du suxaméthonium. L'essai a été réalisé avec la tétra-hydro-aminacrine ("THA") et du suxaméthonium et il s'agissait d'obtenir un relâchement musculaire pendant 1470 interventions chirurgicales. La technique consiste dans l'injection intermittente de faibles quantités de suxaméthonium (10 mg cation) après une dose initiale de THA et du musculo-plégique. La consommation moyenne est de 75 mg cation par heure. La méthode facilite le maintien d'un niveau égal de relâchement grâce aux injections intermittentes de suxaméthonium. On risque de provoquer un blocage neuro-musculaire prolongé en dépassant l'échelle posologique indiquée ici.

ZUSAMMENFASSUNG