THE SUPERIORITY OF TACRINE AS A SUPPLEMENT TO SUXAMETHONIUM*

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Tetrahydroaminacrine (THA, tacrine) consists of 3 benzine rings with 1 carbon atom replaced by a nitrogen atom and another by an amine radical, while 4 carbon atoms each have an additional hydrogen atom. There are no quaternary ammonium radicals to bestow curaremimetic characteristics, such as are found in the molecules of therapeutically related drugs like neostigmine, hexafluorenium and galanthaminum hydrobromide (nivaline), and THA was originally used in medicine as an antagonist of the respiratory and central depression caused by morphine.[1, 2] A monoamine-oxidase inhibitory action of THA has been demonstrated.[11] In Australia[3] and Scandinavia[4, 5] anaesthetists have used THA with notable success to render small doses of suxamethonium long-acting enough to serve as the only relaxant for the common surgical operations. In the USA[6] hexafluorenium (mylaxen) has been used for this purpose, and hexafluorenium has also been used in South Africa.[7]

Both THA and hexafluorenium were subjected to a detailed clinical and experimental investigation by us, but it soon became apparent that hexafluorenium had serious side-effects on the heart and lungs in every case.[8] THA, on the other hand, had no side-effects of importance in our hands. We were impressed by its usefulness, and our experiences of its use in 392 patients is the subject of this paper.

METHODS

In the prepared protocols special mention was made of the following: nature and time of the premedication, body temperature, anaesthetics used, prompt or delayed recovery from relaxation as well as from unconsciousness, upper respiratory secretions, the presence or absence of bronchial constriction, results of the 'acholest' cholinesterase test paper controls, the exact duration of the apnoeas, blood pressure and pulse rate before and after the anticholinesterase, grip strength before and immediately after the anaesthetic, tidal and minute volumes obtained with a Parkinson Cowen dry-gas meter and non-rebreathing valve, and finally the nature of neuromuscular transmission as determined with a peripheral nerve stimulator. At first we used an instrument donated to us by Medical Distributors Ltd., Johannesburg, then the standard, commercially available 'medilec', and finally the prototype of an inexpensive and safe stimulator, which was designed and built by Mr. W. V. McBride of the physiology department of the University of the Witwatersrand (Fig. 1). An electrocardiogram was obtained in 68 cases, usually that from an oesophageal electrode, with all 4 other electrodes fixed to the upper arms as indifferent ones.

Thiopentone was used for induction of anaesthesia in 73% of our cases, and methohexitone in the remainder. Immediately following this, 20 - 50 mg. of suxamethonium was used for intubation of oesophagus and larynx and this first apnoea carefully timed (Fig. 3). On resumption of spontaneous respiration, trichlorethylene was added to the nitrous oxide mixture in 27%, methoxyfluorane in 4% and 0·5% halothane intermittently in all the other cases. THA was always given in a single dose of 15 mg. intravenously to adults, except in 5 patients who received 15 - 60 mg. of tacrine orally and another 5 who received 75 mg. orally for premedication.

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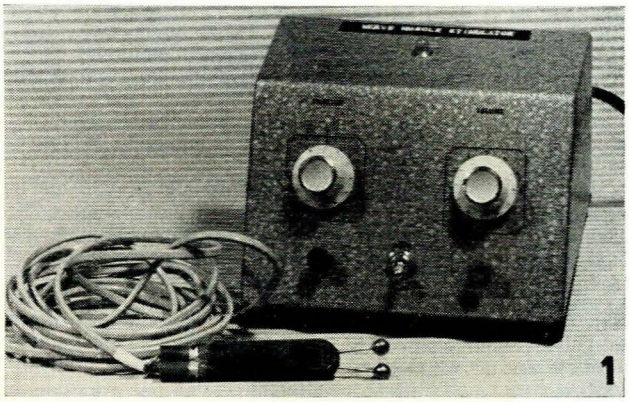

Fig. 1. Nerve muscle stimulator used as a routine procedure in the determination of the type of neuromuscular block.

The grip strength was frequently measured before and just after termination of anaesthesia with an ergometer or an ordinary bladder syringe's rubber bulb attached to any baumanometer (Fig. 2).

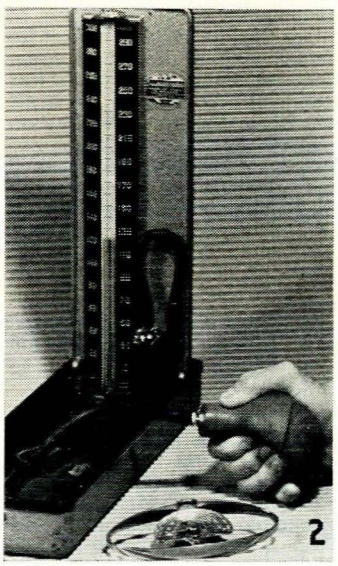

Fig. 2. The instrument used to measure grip strength as an index of the recovery of muscular power post-operatively.

The blood pressure was usually measured by the oscillometric indirect manner, often with the aid of a Boullit or Von Recklinghausen oscilloscope.

THA was given to 18 rats through a plastic cannula tied into the jugular vein. Another cannula fixed into the trachea of the rat was connected to a cylinder of oxygen by means of a rubber tube with an orifice for intermittent occlusion, when artificial respiration was desired. Eighteen experiments were carried out with the gastrocnemius tendon attached to a recording kymograph, and the sciatic nerves were exposed and fixed to stimulating electrodes. In 8 cases the rat's electrocardiogram was recorded throughout.

RESULTS

THA was given to 392 patients altogether, and in not one of these did we encounter notable side-effects. On the contrary, the predictability of the duration of apnoeas after suxamethonium as recorded in Fig. 3, the fact that 20 mg. of suxamethonium resulted in as long an apnoea as 50 mg. of suxamethonium after 15 mg. of THA in the average adult (Fig. 3), and finally the complete recovery of muscle power once spontaneous respirations recurred, was impressive. This was in marked contrast to the patients who received hexafluorenium, in whom we found electrocardiographic abnormalities in every case, and

serious bronchospasm, as well as incomplete recovery of muscular power and ventilation, postoperatively.[8]

The average duration of the apnoeas after 20 mg. suxamethonium repeatedly injected following 15 mg. of THA in the adult was 17, 15, 12, 9 and 5 minutes for the whole series, and a second dose of 10 mg. of THA then restored the sensitivity to suxamethonium.

One of us (J.W.M.) found the first 2 apnoeas were about 2 - 3 minutes less than these average figures when only nitrous oxide and oxygen were used without supplementation.

Gordh and Wahlin[4] also showed that the duration of the respective apnoeas increased by a few minutes in patients with heart disease, hypotension or supplementation with barbiturate; halothane in concentrations above 0·5% markedly prolonged the apnoeas.

Oral THA given an hour pre-operatively proved to be ineffective in doses of less than 75 mg. in the average adult. After this dose (75 mg.) the sensitivity to suxamethonium was roughly the same as in Fig. 3, and no less evanescent. One of these cases had no supplementation to nitrous oxide and oxygen anaesthesia after methohexitone-induction and claimed afterwards to have become aware of her surroundings during her pelvic floor repair. She also had persistent postoperative vomiting, and so we stopped giving THA by the oral route.

Nausea on awakening was noted in 14% and vomiting in 9% of all patients. Persistent vomiting occurred only in the patient already described. Hypotension was never attributed to THA, and salivation did not require any special therapy although it was commented upon in 10% of all patients. Atropine was only used in very long anaesthesia after 45 mg. or more of THA, although the pulse rate commonly dropped to 60 per minute or below when no atropine was used in the premedication. The electrocardiograms showed a bigeminy in 1 instance after THA in a patient deeply anaesthetized with halothane; irregularly spaced systoles with an evanescent nodal rhythm were recorded in 8 patients; in 59 no abnormality was seen after THA. After suxamethonium a slowing of the heart rate occurred invariably, and even after atropine premedication within the previous hour this was striking. Two children aged 5 and 7 respectively, who had received atropine more than 2 hours before, had heart rates of below 40 per minute briefly after the fourth and third doses of 20 mg. of suxamethonium respectively, and each had a period of asystole just longer than 3·0 seconds (see Fig 4).

Records made of the tidal and minute volumes before and after the intravenous administration of THA revealed no consistent change; they remained the same in anaesthetized patients. Once the apnoea from suxamethonium had worn off, the minute volumes promptly reached control values in all 15 instances in which this was recorded.

The grip strength was most conveniently measured by the use of an ordinary large rubber bulb from a bladder syringe connected to any baumanometer (Fig. 2). In contrast to the patients who had been given hexafluorenium (mylaxen), and whose average readings were below 50 mm.Hg, and who commonly had bronchospasm audible on auscultation, the patients who had been given THA were quite free of residual weakness and bronchospasm. The arithmetic mean of the grip strength was 180 mm.Hg in 87 adult patients, with a median reading of 150 mm.Hg. The low median was caused by exceptional instances of unnecessarily deep halothane or a methoxyfluorane anaesthesia.

THA was used in 24 caesarean sections, and the Apgar scores of the infants were probably higher than in cases where THA was not used, although this can only be proved by a larger well-controlled trial.

Particularly after short anaesthetics there was no delay in awakening; the recovery was usually so prompt and complete as to be a nuisance occasionally. Stimulation of the ulnar nerve at the wrist always caused the fingers to move rhythmically at the end of the operation; the contraction was well sustained, and we did not encounter post-tetanic fasciculation or other evidence of dual block in anyone after THA and intermittent injections of 20 mg. of suxamethonium or less. Again, this was not the case in patients who had been given hexafluorenium. This finding encouraged us to use THA in poor-risk people with intestinal obstruction, and although some of these patients were old and suffering from severe fluid and electrolyte disturbances, none had postoperative ventilatory difficulties.

Results with the acholest test paper method for simple and quick pseudocholinesterase determinations[10] revealed that both THA and hexafluorenium resulted in a serum cholinesterase activity still in the 7 - 18 minute 'normal' bracket. A strongly decreased serum cholinesterase activity was encountered 6 times in patients with severe liver disease; they were all given THA and suxamethonium, and the resulting apnoeas were only longer by approximately 30%.

DISCUSSION

It is not enough to have a patient breathing at the end of an operation, and even the restoration of the pre-operative minute-volume of respiration can be hazardous if the patient is unable to take a deep breath or cough productively. Such ventilatory reserve can be discerned by methods which require the cooperation of the patient such as the recording of the vital capacity. In the preliminary trials reported in this paper we were impressed by the weakness and lack of ventilatory reserve of our patients after undergoing routine surgery under orthodox anaesthesia with non-depolarizing relaxants; in these cases we could always show a poorly sustained twitch with a fade and post-tetanic fasciculation after they were considered fully recovered by the anaesthetist. This finding was significant because it did not depend on cooperation from the patient.

When we gave hexafluorenium to 66 patients to act as a control for the assessment of THA as an extender of suxamethonium-relaxation, we found the same weakness present in our patients postoperatively, with 1 striking difference. Most of our patients who had received non-depolarizing relaxants could be restored to a satisfactory state as regards strength and ventilatory reserve with adequate doses of neostigmine. On the contrary, no change was noted when neostigmine was used to treat the weak state we often encountered postoperatively after hexafluorenium. This evidence of a dual block after hexafluorenium is not unexpected, because hexafluorenium is a muscle relaxant in its own right,[6] and its potent depressant effects on the cardiovascular system[8] can be understood in the light of its chemical relationship with hexamethonium.

THA has none of these disadvantages of hexafluorenium. Apart from its mild stimulating action on the central nervous system,[1, 2] and its anticholinesterase action, we did not find evidence of any other pharmacological action, in marked contrast to the numerous side-effects of hexafluorenium.[8] It is known that THA possesses a mild stimulating effect on the intestinal tract, and it was our impression that the bowels were as constricted after THA as they are during spinal analgesia. Whereas we previously regarded all muscle relaxants as at least relatively contraindicated in patients with intestinal obstruction, we now use THA as a routine medication in these cases in conjunction with small doses of suxamethonium.

After the intravenous administration of THA the optimum intermittent dose of suxamethonium is 20 - 25 mg. This point is clearly illustrated in Fig. 3 where each column represents the duration of apnoea after, firstly, 50 mg. of

suxamethonium, and then the apnoeas after THA priming. The shaded portions of the columns represent the duration of the apnoeas as found by Gordh and Wahlin[4] after 10 mg. of THA and repeated doses of 50 mg. of suxamethonium. We gave 15 mg. of THA and followed this by repeated doses of only 20 mg. of suxamethonium; in spite of giving less than half the dose of Gordh, all our apnoeas actually exceeded in duration those of Gordh and Wahlin, except the sixth one which is marked by 'ears' in Fig. 3. Our other apnoeas are indicated by the broken-line extensions.

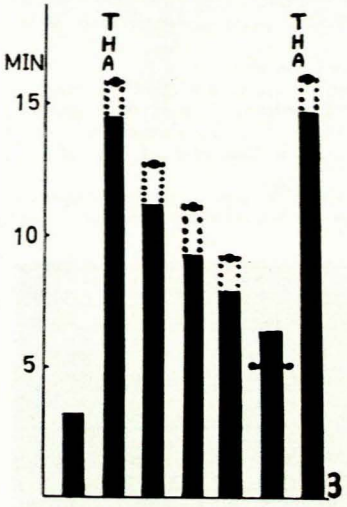

Fig. 3. See text.

Perhaps even more important evidence was obtained with the electrocardiograph. After the injection of 20 mg. suxamethonium in an adult, and proportionately less in children, we did not find any marked change in the ECGs of 68 patients. This is in striking contrast to the usually impressive arrhythmias associated with the repeated use of larger doses of suxamethonium, illustrated in Fig. 4, and previously described by Lupprian and Churchill-Davidson.[9]

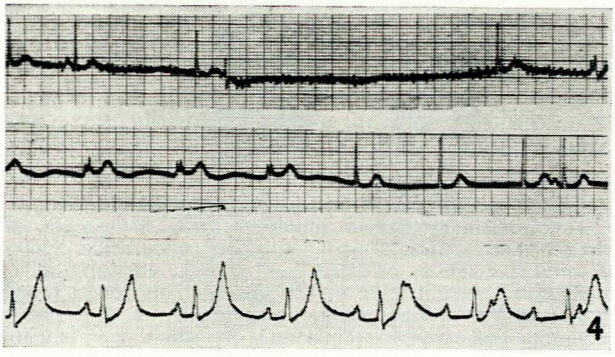

Fig. 4. Top: Brief asystole after the injection of a third dose of 25 mg. of suxamethonium in a child of 3 years. Note slight baseline interference caused by occult shivering, abolished in the second tracing which followed the top directly; an evanescent ventricular conduction defect is also apparent. *Bottom*: Wenckebach's periodicity after the fifth dose of 50 mg. of suxamethonium in a 17-year-old during halothane anaesthesia.

It is therefore clear that THA has rendered the use of intermittent suxamethonium safer, and it has extended its scope tremendously.

Two important reservations to the use of THA are, firstly, the routine preliminary need of atropine, particularly in the young, and secondly, an amino-oxidase inhibitor such as THA should not be given with pethidine, since the combination[12] may lead to central sympathetic and psychic overstimulation with anxiety, severe headache, constriction of the chest, and tachycardia.

SUMMARY

Clinical trials of THA (tacrine, tetrahydroaminacrine) in a new combination with suxamethonium established the safety and usefulness of THA in extending the duration of controlled relaxation with much-reduced doses of suxamethonium, with predictable and complete recoveries as compared with the similar employment of hexafluorenium. The conclusion that THA is superior to hexafluorenium is based on an extensive clinical investigation as well as animal studies which both revealed numerous undesirable side-effects of hexafluorenium, and an impressive lack of side-effects in patients who received THA under surveillance with the electrocardiograph, spirometer and peripheral nerve stimulator.

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