TETRAHYDROAMINACRINE IN ANAESTHESIA

BY

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SUMMARY

Tetrahydroaminacrine was found to produce little more than fleeting improvement of the respiratory depression due to morphine in rabbits. It had no significant effect on the respiratory minute volume in premedicated anaesthetized man. It had a mild cardio-inhibitor action in the anaesthetized patient but in those premedicated with atropine, the intensity of the effect was slight, unlike that of neostigmine. Tetrahydroaminacrine was not capable of protecting mice against lethal doses of gallamine triethiodide and was relatively unsatisfactory as an antidote to curarization in man.

Tetrahydroaminacrine (1:2:3:4-tetrahydro-5-aminoacridine hydrochloride) was first examined in detail as a substance with useful pharmacological actions by Shaw and Bentley (1949). Essentially they found it to be an analeptic producing rapid arousal of morphinized dogs and cats though it had comparatively little effect on rabbits. (These latter animals, however, had been given relatively astronomical doses of morphine of the order of 200 mg/kg.) Tetrahydroaminacrine is also said to be an effective analeptic in man (Shaw, 1960; Stone, Moon and Shaw, 1961; Gordh and Wåhlin, 1961). Tetrahydroaminacrine is an anticholinesterase (Shaw and Bentley, 1955; Heilbronn, 1961) and protects rats against the respiratory paralyzing effect of tubocurarine; it reverses curarization in dogs (Gershon and Shaw, 1958), and in anaesthetized patients (Temmeline quoted Gordh and Wåhlin, 1961; McCaul and Robinson, 1962).

Tetrahydroaminacrine prolongs the action of suxamethonium (Crankshaw, 1960, quoted Beneviste and Dryberg, 1962; Gordh and Wåhlin, 1961). Barrow and Smethurst (1963) were particularly successful in the employment of tetrahydroaminacrine with suxamethonium and report that the duration of a single dose of the latter was prolonged to 15 minutes. Similar conclusions were reached by Hugin (1962) and by Smart (1964). Barrow and Smethurst caution against the risk of bradycardia as a result of the administration of tetrahydroaminacrine to potentiate suxamethonium and give atropine as a routine immediately before producing relaxation.

In general tetrahydroaminacrine ought, therefore, to find a wide application in anaesthesia. Firstly, it should be of value in reversing opiate-induced respiratory depression. Secondly, because the drug possesses both analeptic activity and ability to reverse curarization, it should be of special value in restoring the breathing of curarized patients. Thirdly, it was expected that it could satisfactorily be employed to prolong the action of suxamethonium in cases where relaxation lasting some 15 to 30 minutes was required. A few trials in these fields cast some doubt on the early conclusions about its usefulness. Its action was therefore investigated in some detail.

METHODS

Analeptic activity.

This was studied in unanaesthetized rabbits which had been given morphine 8 mg/kg intravenously 10 minutes before. Respiratory rate and minute volume were recorded before and after morphine for at least 30 seconds with the aid of a Gaddum (1941) respiration recorder and continuous records were made for 3 to 5 minutes after the intravenous administration of tetrahydroaminacrine. A dosage level of 3 mg/kg was chosen after 5 and 4 mg/kg had been found to cause convulsions.

The analeptic activity of tetrahydroaminacrine was studied in human subjects who had been premedicated with an opiate (pethidine 50 or 100 mg, or morphine 10 mg) and with atropine 0.6 mg. Anaesthesia had been induced some 15 minutes prior to the injection of the tetrahydroaminacrine.
by a sleep dose of thiopentone, i.e. just sufficient to abolish the eyelash reflex, together with the suxamethonium (5 mg/stone; 0.8 mg/kg). The patient's larynx, trachea and larger bronchi were then sprayed with 4 per cent lignocaine with the aid of a Macintosh spray. Auffed endotracheal tube was then passed and the cuff inflated. Thereafter anaesthesia was stabilized on nitrous oxide, oxygen and halothane using 1 per cent of halothane vapour delivered by a Fluotec calibrated vapourizer. Respiratory minute volumes were recorded with the aid of a Wright respirometer placed between the expiratory valve and the catheter mount and consecutive readings were made at the completion of each minute. At least three readings preceded the administration of tetrahydroaminacrine.

The antagonism between tetrahydroaminacrine and tubocurarine was studied in patients who had been anaesthetized by the technique outlined above but the halothane was turned off at least 5 minutes before tetrahydroaminacrine was given. Respiratory minute volume was determined in the same manner as above. Respiration had been controlled during the period of curarization. It was therefore restarted when necessary by the use of carbon dioxide. (This was entirely logical because the patient had been hyperventilated. Further, in a number of other patients who had been studied by continuous electrocardiography during the process of restoration of breathing by carbon dioxide no changes, apart from a slight increase in pulse rate, had been observed.) Respiratory minute volumes were recorded for at least 2 minutes before the administration of the antidote which was then injected intravenously into an upper limb vein towards the end of the next minute. The recording of respiratory minute volumes during the period of skin stitching was avoided as it had been found in previous studies (Hunter, unpublished) that this kind of stimulation increases the depth of breathing. In addition, four records of respiratory minute volume were made at the end of neurosurgical operations with a "bag in a bottle" recorder (Brennan, 1956).

The criteria for the assessment of the severity of the curarization of these cases were those used in a previous study (Hunter, 1957). Patients with "profound" curarization had a visibly inadequate tidal volume; respiration was entirely diaphragmatic and chin-tugging prominent. Those with “moderate" curarization had a mild degree of respiratory depression and the pattern of the bag movement was that described by Morton (1950) as "square", i.e. instead of there being the normal pause between expiration and inspiration, the pause in the respiratory cycle took place between the end of inspiration and the start of expiration. These patients had visible "rocking boat" breathing movements. Tidal volume was such that they did not tend rapidly to become cyanosed on an oxygen-rich mixture, though breathing was definitely inadequate and the patients became a little blue when breathing air. In those with “mild” curarization, chin-tugging was present but the respiratory minute volume was apparently adequate and there was no tendency to the development of cyanosis. The pattern of the respiratory movements, however, was disturbed and there was some visible indrawing of the upper chest in inspiration. Such patients did not cough vigorously when a suction catheter was passed down into contact with the unanaesthetized area of the bronchi.

The criteria of complete decurarization were the restoration of the normal pattern of respiratory movements, the return of an adequate tidal volume and the ability to cough vigorously and contract the abdominal muscles in response to the passage of a suction catheter down into the unanaesthetized bronchi or to vigorous movements of the endotracheal tube.

In patients in whom tetrahydroaminacrine was used to prolong the action of suxamethonium the anaesthesia was conducted as outlined above. Some of these cases were premedicated with papaveretum 20 mg and hyoscine 0.4 mg. Atropine 0.3 mg was given with the thiopentone in these patients to prevent the severe bradycardia which often occurs when halothane is administered to those premedicated with hyoscine.

Tetrahydroaminacrine 15 mg was injected just before the start of the operation. When relaxation became necessary, usually some 2 to 5 minutes later, suxamethonium 30 mg was injected intravenously.

Pulse rates were counted for at least 15 seconds at intervals of 2 minutes after the injection of tetrahydroaminacrine or suxamethonium until they had reached a steady level. The arterial pressure was determined by the pressure in a sphygmmomanometer cuff necessary to obliterate the radial pulse.
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RESULTS

Action on Respiration.

Laboratory studies.

Tetrahydroaminacrine produced an improvement in respiratory minute volume and a less marked and rather inconsistent improvement in respiratory rate when given to rabbits morphinised by the intravenous injection of 8 mg/kg of this drug (table I). The action was, however, evanescent and within 5 minutes had gone completely. This effect was obtained with a dose of 3 mg/kg of tetrahydroaminacrine. Larger doses produced convulsions. There was an obvious improvement in the wakefulness of the animals which lost the rather "hangdog" appearance characteristic of the heavily morphinized rabbit. By comparison with other analeptics this degree of reversal is poor. Nikethamide in a dose of 25 mg/kg will produce a more effective reversal which lasts for some 25 to 30 minutes, while nalorphine in a dose of 1 mg/kg reverses the action of morphine (8 mg/kg) in rabbits completely and the reversal persists for at least 1½ hours (Hunter, in preparation).

Studies in man.

When tetrahydroaminacrine 15 mg/kg was injected intravenously into patients premedicated with an opiate and anaesthetized with nitrous oxide, oxygen and halothane no consistent increase in respiratory minute volume was observed (fig. 1). A similar result was obtained when records of respiration were made with the "bag in a bottle" recorder.

Action on the Cardiovascular System in Man.

The administration of tetrahydroaminacrine to prolong the action of suxamethonium afforded an opportunity to study its effects on pulse rate. Pulse rates and blood pressure were also followed in those in whom the drug was given for the reversal of curarization. In thirty-three patients premedicated with morphine or pethidine and atropine, the intravenous injection of tetrahydroaminacrine 15 mg produced a fall in pulse rate of 5.6±7.2 beats per minute. When in fourteen patients the dose of tetrahydroaminacrine was increased to 30 mg (for the reversal of curarization) the pulse rate decline was slightly less, 4.6±4.6 beats per minute, but not significantly so (fig. 2). In eight patients premedicated with papaveretum and hyoscine, the decline in pulse rate following the administration

<table>
<thead>
<tr>
<th>Table I</th>
</tr>
</thead>
<tbody>
<tr>
<td>The changes in respiratory minute volume and respiratory rate produced by tetrahydroaminacrine (3–5 mg/kg) in 8 morphinized rabbits.</td>
</tr>
<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Respiratory minute volume (per cent control)</td>
</tr>
<tr>
<td>After 8 mg/kg morphine</td>
</tr>
<tr>
<td>Respiratory rate (per cent control)</td>
</tr>
<tr>
<td>52 (33–70)</td>
</tr>
<tr>
<td>74 (37–110)</td>
</tr>
</tbody>
</table>

Fig. 1

The effect of tetrahydroaminacrine on the respiratory minute volumes of anaesthetized patients. The open circles indicate the effect of tetrahydroaminacrine 15 mg, the black dots show the changes produced by tetrahydroaminacrine 30 mg. Note that the drug was substantially without effect.
The pulse rate changes produced by tetrahydroaminacrine.

I. Tetrahydroaminacrine 15 mg in patients premedicated with morphine 10 mg or pethidine 50-100 mg and atropine 0·6 mg.

II. Tetrahydroaminacrine 30 mg to reverse curarization in patients premedicated with morphine or pethidine and atropine.

III. Tetrahydroaminacrine 15 mg in patients premedicated with papaveretum 20 mg and hyoscine 0·4 mg.

of tetrahydroaminacrine 15 mg was a little more marked, being of the order of 12 beats/min (fig. 2).

The subsequent administration of suxamethonium produced a variable response in the pulse rate. In twelve out of seventeen cases premedicated with atropine, the change noted was within the likely error of counting (±4 beats per minute). Others, however, showed falls in pulse rate of up to 52 beats/min (fig. 3). In one such case the pulse rate abruptly halved itself after the administration of suxamethonium. Another patient in whom the pulse rate changes were not followed in detail was found to be pulseless after the injection of tetrahydroaminacrine followed by suxamethonium. Both these last cases responded to the intravenous injection of atropine.

Tetrahydroaminacrine had no significant effect on the arterial pressure. In this study there was a rise of 2·4±5 mm/Hg in nineteen patients to whom 15 mg were given. The administration of tetrahydroaminacrine and suxamethonium was followed by an overall increase in blood pressure of 13±13 mg/Hg (table II). An almost identical result was obtained in a previous study of cases in which patients given tetrahydroaminacrine and suxamethonium were compared with others who had received tubocurarine and diallylnortoxiferine (Hunter, 1964). The overall changes in pulse rate with tetrahydroaminacrine and suxamethonium were again somewhat variable. In general, slowing occurred except when atropine was given also. As
TABLE II
The blood pressure changes associated with muscular relaxation with tetrahydroaminacrine and suxamethonium in patients anaesthetized with nitrous oxide, oxygen and halothane.

<table>
<thead>
<tr>
<th>Relaxant</th>
<th>Blood pressure (mm Hg)</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetrahydroaminacrine and suxamethonium (with or without atropine)</td>
<td>Before: 113±24, After: 126±31, Change: +13±13</td>
<td>28</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>Before: 111±27, After: 89±24, Change: -22±11</td>
<td>8</td>
</tr>
</tbody>
</table>

The very small control series for tubocurarine was analyzed to show that these figures were from the same population as the series for diallylnortoxiferine where 2 mg/stone of tubocurarine produced a blood pressure fall of 24±23 mm Hg in comparable circumstances (Hunter, 1964).

with tetrahydroaminacrine alone, the fall in pulse rate was greater in those premedicated with papaveretum and hyoscine than in those who had received morphine and atropine (fig. 4).

Anti-curare Activity.

Laboratory studies.

It had previously been observed (Hunter, 1955) that 5mg/kg of gallamine triethiodide was approximately an LD95 when the drug was given by the intravenous route to mice. The administration of neostigmine 0-2 mg/kg with atropine 0-2 mg/kg in the same syringe protected a significant proportion of the animals. It was confirmed that these findings applied in the batch of mice weighing about 30 g selected for study.

The toxicity of tetrahydroaminacrine by the intravenous route in these animals was determined. It seemed that the LD50 lay between 5 and 10 mg/kg (table III). The administration of 0-2 mg/kg of atropine protected the mice against the lethal effects of tetrahydroaminacrine to some extent and made possible the administration of 10 mg/kg with appreciably less mortality.

Attempts were then made to protect mice against a dose of 5 mg/kg of gallamine with the aid of 5 mg/kg of tetrahydroaminacrine without atropine and 10 mg/kg tetrahydroaminacrine with 0-2 mg/kg of atropine. No significant protection was observed at either dosage level.

Studies in man.

Twenty-three patients were given tetrahydroaminacrine in a dose of 30 mg at the conclusion of an operation to reverse curarization produced by tubocurarine. The results are given in table IV where it will be seen that in the presence of mild curarization tetrahydroaminacrine was a relatively
effective antagonist. In those with moderate curarization it was unreliable, and in those with profound curarization it had little effect. Neostigmine successfully completed the decurarization when tetrahydroaminacrine had been inadequate.

**TABLE III**
The protection of mice against lethal doses of gallamine by neostigmine and tetrahydroaminacrine.

<table>
<thead>
<tr>
<th>Dose mg/kg</th>
<th>Mice used</th>
<th>Mice died</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetrahydroaminacrine</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Tetrahydroaminacrine</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Tetrahydroaminacrine</td>
<td>10</td>
<td>0-2</td>
</tr>
<tr>
<td>Tetrahydroaminacrine</td>
<td>20</td>
<td>0-2</td>
</tr>
<tr>
<td>Gallamine</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Gallamine</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Tetrahydroaminacrine</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Gallamine</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Tetrahydroaminacrine</td>
<td>0-2</td>
<td>Atropine</td>
</tr>
<tr>
<td>Gallamine</td>
<td>5</td>
<td>0-2</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>0-2</td>
<td></td>
</tr>
</tbody>
</table>

* $\chi^2 = 5-45$; $P > 0.01 < 0.02$. † $\chi^2 = 5-49$; $P > 0.01 < 0.02$.

The respiratory minute volumes of eleven of the patients studied are given in table V where it will be seen that the administration of tetrahydroaminacrine did produce a substantial improvement in ventilation (fig. 5). In fact in some cases it restored what seemed to be an adequate respiratory minute volume. The pattern of respiration, nevertheless, remained disorganized with persistent indrawing of the upper chest. Two patients in whom 30 mg of tetrahydroaminacrine had not produced satisfactory decurarization were given an additional 15 mg of the drug, but no further recovery was observed.

**DISCUSSION**
The work which is here reported, in general casts doubt on the original justification for the introduction of tetrahydroaminacrine as an analeptic and decurarizing agent, but though the drug has been a disappointment in these respects it does not follow that it is useless. Indeed the author's experience while using tetrahydroaminacrine to prolong the action of suxamethonium, has suggested that this particular method of obtaining muscular relaxation is less likely to cause blood pressure disturbance than any other, and for this reason the place of
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511

30 mg THA

TIME (min)

1

FIG. 5

The effect of tetrahydroaminacrine 30 mg on the respiratory minute volumes of curarized patients. Where the lines become broken instead of continuous, a dose of neostigmine and atropine was given to complete inadequate reversal of curarization.

tetrahydroaminacrine in the practice of anaesthesia ought to be assured. The work which has been done, however, does cast some light on the overall action of the drug.

The finding that tetrahydroaminacrine was not a particularly effective analeptic was not wholly unexpected. Some years previously amiphenazole had been introduced as an analeptic to prevent the respiratory depression associated with the administration of morphine. It has been found by the author (unpublished data) to be considerably inferior for this purpose to nikethamide. It seemed from various reports, that tetrahydroaminacrine had properties similar to those of amiphenazole. Indeed an elevation of mood of morphinized patients has been reported by Simpson and his colleagues (1960) similar to that noted by the author in the rabbits with both drugs. The existence of this action poses a clinical problem directly related to anaesthesia. If tetrahydroaminacrine has a similar action in the anaesthetized subject to that in the morphinized rabbit, is it possible that its administration may add to the likelihood that a paralyzed patient may become conscious during anaesthesia while still paralyzed? It would seem that this risk is very remote when nitrous oxide, oxygen and halothane are used, but what would be the situation with nitrous oxide and oxygen anaesthesia alone (as, for example, for Caesarean section) is not at all clear.

The apparent lack of muscarinic activity of tetrahydroaminacrine was surprising, because it is stated to have an anticholinesterase activity comparable to that of neostigmine (Heilbronn, 1961), yet it obviously does not exert a comparable action either on the heart or on the mucous glands, in man at least. It is, however, interesting that the mice which died as a result of the administration of tetrahydroaminacrine undoubtedly had hyperactivity of the bowel and bladder, considerable glandular secretion and sweating. No immediate explanation of the differences in the two species is, however, immediately apparent. It may be that differential solubility in particular tissues is responsible, but this is pure speculation.

The immediate consequence of the relative lack of cardio-inhibitor action of tetrahydroaminacrine seems to be that there is no need to give atropine with tetrahydroaminacrine in the patient who has already been premedicated with this drug. It is, however, important to be quite certain that the atropine has been given at an appropriate time because the more serious declines in pulse rate noted in the course of this work were in patients premedicated with morphine and atropine some 2 hours before the administration of tetrahydroaminacrine. In those premedicated with papaveretum and hyoscine in whom a decline in pulse rate of something up to 20 beats/min is to be anticipated, the need for giving atropine before tetrahydroaminacrine is obvious.

The muscarinic activity of tetrahydroaminacrine is not, however, the only indication for the use of atropine. It is generally accepted that the repeated administration of suxamethonium is liable to produce cardiac disturbances in patients under general anaesthesia (Lupprian and Churchill-
The pulse rate changes following the administration of tetrahydroaminacrine 15 mg with atropine 0.3 mg in patients under the influence of nitrous oxide, oxygen and halothane anaesthesia.

<table>
<thead>
<tr>
<th>Premedication</th>
<th>Cases</th>
<th>After THA 15 mg with atropine 0.3 mg</th>
<th>After subsequent suxamethonium</th>
<th>Overall change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine or pethidine and atropine</td>
<td>20</td>
<td>3.6 ± 6.9</td>
<td>4.8 ± 9.6</td>
<td>8.4 ± 10.0</td>
</tr>
<tr>
<td>Papaveretum and hyoscine</td>
<td>16</td>
<td>−0.4 ± 5.7</td>
<td>1.5 ± 4.5</td>
<td>1.1 ± 6.7</td>
</tr>
</tbody>
</table>

These disturbances are normally of the nature of a sinus bradycardia and it is probably significant that there was not as a rule further decline in pulse rate when suxamethonium was given after tetrahydroaminacrine. In two instances major cardiac disturbances did occur and it may well be that the administration of a small dose of atropine with the tetrahydroaminacrine is in fact desirable to prevent muscarinic responses to repeated doses of suxamethonium. On the other hand, in the early cases of the series atropine 0.6 mg was given, as described by Barrow and Smethurst (1963), routinely with tetrahydroaminacrine. The result in many cases was a pulse rate of the order of 90–100 beats/min, and this combined with an unchanged blood pressure not infrequently led to increased wound bleeding.

On the other hand, the risk of muscarinic effects in patients given tetrahydroaminacrine and suxamethonium is so serious that the author now feels that atropine 0.3 mg should be given to every patient with the tetrahydroaminacrine.* If tetrahydroaminacrine is to be used to reverse curarization, however, the risk of muscarinic effects in those already premedicated with atropine does not seem to be sufficiently serious to make the routine administration of atropine necessary.

Finally the fact that tetrahydroaminacrine, with an anticholinesterase activity nearly equal to that of neostigmine, does not possess an antichure activity of comparable magnitude, calls for comment. This was not, however, altogether surprising because phystostigmine is by no means as effective an antidote to curarization as is neostigmine (Hunter, 1955). Indeed, in the paper quoted, the author suggested that neostigmine had a dual action in reversing curarizing drugs. The urethane tail of the drug gives it to anticholinesterase properties. The quaternary nitrogen atom attached to the phenol ring, as in edrophonium, seems to be capable of making the myoneural junction more sensitive to acetylcholine, independently of any cholinesterase activity. It is, too, well recognized that the anticholinesterase activity of edrophonium is not sufficient to account for its power to reverse curarization (Kuperman, Gill and Riker, 1961), though at one time it was felt that this was the mechanism by which this drug produced its effects (Hobbiger, 1952).

ACKNOWLEDGMENT
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REFERENCES
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