ANTIDOTES TO "TRUE" CURARIZING AGENTS
including a report on Ro 2-3198 (Tensilon)

By A. G. DOUGHTY and W. D. WYLIE

THE need for an antidote to curare-like substances may arise clinically in the following circumstances:

1. To restore full respiratory activity at the end of an operation.
2. To reverse curarization in an unexpectedly short operation, e.g. when prolonged surgery is intended but found to be impracticable.
3. Following a short procedure during which almost complete paralysis of the patient has been necessary.
4. To abolish curarization in a patient who has shown an unusual sensitivity to curarizing drugs, e.g. latent myasthenics.
5. To abolish the occasional long-lasting mild sequelæ of curarization.

Neostigmine is well established as an effective antidote, but it has marked side effects which, while not precluding its use in anaesthesia, justify a search for an equally efficient drug without them.

Randall (1950) investigated a series of 27 compounds for anti-curare activity. Of these he selected two which appeared to approach the ideal of maximum antidotal effect with minimal side-actions. These compounds are known as Ro 2–2561 and Ro 2–3198, the latter being available in the U.S.A. under the trade name of Tensilon. They are closely related to neostigmine, but
they lack the dimethyl carbamic side-chain which is considered to be responsible for the anticholinesterase activity of the latter.

In animal experiments Randall found that these substances possess \( \frac{1}{2} \) the potency of neostigmine as anticurare agents but appear to have a much less marked stimulating action on the parasympathetic system. In experiments on the electric eel their anticholinesterase activity is only 1/100 that of neostigmine. MacFarlane et al. (1950) report that Ro 2-3198 is only 1/1000 to 1/500 as potent as neostigmine in inhibiting rat's brain cholinesterase. These data suggest that a safer antidote than neostigmine is available, since the disadvantages of neostigmine arise from its powerful muscarinic action.

**CLINICAL TRIALS OF NEOSTIGMINE AND RO 2-3198 (TENSILON)**

The advantages and disadvantages of any antidote to a muscle relaxant may be crudely assessed on clinical grounds. That this should be so is important, since the final test of efficiency must be against the background of clinical use. Neostigmine, adequately buffered by atropine sulphate, now occupies a definite place in anaesthesia where muscle relaxants of curariform action are used. By clinically accepted standards it leaves little to be desired as an antidote, but its side effects are considerable and may be
dangerous in certain circumstances. These side effects are noticeable in conscious individuals, and can be assessed on such a person by simple comparison with other drugs of like type. It is also possible to gain some idea of the efficiency of an antidote against a known dose of muscle relaxant on a conscious person.

**Conscious Subjects**

Experiments on conscious subjects were carried out with two objects in mind: first, to record the side effects of clinical doses of neostigmine with and without atropine, and by comparison with these results to assess Ro 2–3198 (Tensilon); second, assuming that the new drug offered certain advantages over neostigmine in regard to these side effects, to assess its value as an antidote against a curarizing agent and by comparison with neostigmine.

The table shows the results of injecting known doses of an antidote into conscious subjects. Subjective symptoms were almost entirely limited to fasciculation of muscles, to epiphora, salivation and intestinal stimulation. Objectively the pulse rate was recorded. In doses up to as much as 20 mg. of Ro 2–3198 symptomatic manifestations were never more than slight, and rapidly passed off, whereas with a dose of 1.25 mg. of neostigmine, previously covered by 1.3 mg. of atropine sulphate, just as obvious manifestations were noticed though with this dose they did not persist. With either drug some degree of bradycardia was present, and this lasted for a longer period than the subjective sensations. Unbuffered neostigmine produced markedly severe and prolonged reactions.

In attempting to assess the efficacy of Ro 2–3198 as an antidote, a dose of gallamine triethiodide (Flaxedil), sufficient to produce diplopia and weakness of the small
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Effects of Ro 2–3198 (Tensilon) and Neostigmine on Conscious Subjects.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Drug</th>
<th>Dose mg.</th>
<th>Symptoms</th>
<th>Duration in minutes</th>
<th>Pulse change</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>Ro 2–3198</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>Ro 2–3198</td>
<td>5</td>
<td>+</td>
<td>3</td>
<td>6/min.</td>
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<tr>
<td>A</td>
<td>Ro 2–3198</td>
<td>10</td>
<td>+</td>
<td>5</td>
<td>10/min.</td>
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<tr>
<td>B</td>
<td>Ro 2–3198</td>
<td>10</td>
<td>+</td>
<td>3</td>
<td>12/min.</td>
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<tr>
<td>A</td>
<td>Neostigmine</td>
<td>2.5</td>
<td>++ +</td>
<td>45+</td>
<td>12/min.</td>
</tr>
<tr>
<td>A</td>
<td>Neostigmine</td>
<td>1.25</td>
<td>+</td>
<td>10</td>
<td>8/min.</td>
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<td></td>
<td>atropine sulphate</td>
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<tr>
<td>A</td>
<td>Neostigmine</td>
<td>2.5</td>
<td>++</td>
<td>20</td>
<td>12/min.</td>
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<td></td>
<td>atropine sulphate</td>
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</tr>
<tr>
<td>B</td>
<td>Neostigmine</td>
<td>2.5</td>
<td>++</td>
<td>35</td>
<td>14/min.</td>
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<td>atropine sulphate</td>
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muscles of the hands, was given intravenously. This averaged 40–50 mg. Ro 2–3158 or neostigmine was given later, either within two minutes of the onset of curarization or after approximately 15 minutes had passed and the paralyzing effect was rapidly passing. In the former case it was found that the effective dose of Ro 2–3198 was between 15 and 20 mg. but that with this dose there was a liability to revert to partial muscle paralysis after 10–15 minutes. It is emphasized that the assessment of paralysis and the reversal to partial paralysis was made on a purely subjective basis and largely upon ocular imbalance, which is, however, the earliest symptom of curarization and the last to disappear on recovery. Nevertheless, in comparison with doses of neostigmine varying from 1.25 mg. to 2.25 mg. the prolonged effect of Ro 2–3198 was unsatisfactory.
When given 15 minutes after the gallamine, clinically it was as effective as neostigmine.

**During Anaesthesia**

Clinical assessment of Ro 2–3198 during anaesthesia was made on two types of case. First, when a high concentration of curarizing agent was known to be present in the patient, and second, at the termination of an operation when curarization was still apparent. Electro-convulsive therapy with full muscle relaxation was chosen for the first series. The second series was made up of operations during which a muscle relaxant was used and at the termination of which curarization persisted.

For electro-convulsive therapy the procedure was to use a full paralysing dose of a relaxant after a sleep dose of thiopentone and premedication with atropine sulphate. Such a dose, when gallamine triethiodide is used, averages 140 mg. for a female and 160 mg for a male. After the convulsion, and following the period of apnoea succeeded by attempted spontaneous respiration, it is usual to inject 2.5 mg. of neostigmine and to repeat this if necessary. In a series of thirteen cases, Ro 2–3198 was used in place of neostigmine. Dosage was started at 20 mg. and additional doses up to a maximum of 45 mg. were given. In later cases as much as 40 mg. were given at once. In no case was the subsequent respiration considered adequate, and in every case neostigmine was used when the failure of Ro 2–3198 became apparent. The addition of neostigmine produced clinically marked improvement in every case, and the improvement was sustained.

In the second series, Ro 2–3198 was used on over 50 occasions to restore the tone of the abdominal musculature and thoracic respiration at the end of abdominal operations.
in which either d-tubocurarine chloride or gallamine triethiodide was used as the relaxant. In view of the limited effects noted on conscious subjects it was not given with atropine sulphate. The effectiveness as an antidote was judged clinically by hardening of the abdominal muscles and restoration of thoracic respiratory activity.

In those cases in which a relatively small dose of relaxant was given at the beginning of the operation and there were no supplementary doses, the antidotal effect appeared to be complete and recession to the curarized state did not occur. When multiple doses of relaxant were given during the operation the effect of Ro 2-3198 was not reliable: in some cases there was a satisfactory response and no apparent recession to the curarized state, while in others, after an initial response, thoracic respiration appeared to diminish again. The least satisfactory cases were those in which a dose of relaxant was given to facilitate closure of the peritoneum. The Ro 2-3198 would in these cases be given about five minutes after the relaxant.

An attempt was made to assess the effect of the drug on the parasympathetic system. In no case was there excessive salivation or bronchial secretion following its administration in spite of the absence of atropine sulphate. In view of the fact that many of the cases had been given pethidione during the operation its atropine-like action may be responsible for the absence of effects which other workers have observed.

The heart rate was slowed in all cases but the blood pressure remained constant following Ro 2-3198. The fall in pulse rate was greatest when the drug was used to counter the effects of gallamine triethiodide in contrast to d-tubocurarine chloride. This might be expected as the
production of tachycardia is a recognized side-action of the former relaxant.

ASSESSMENT OF RO 2-3198 (TENSILON)

From clinical experience and from experiments on the conscious subject certain conclusions concerning Ro 2–3198 as an antidote to the curarizing agents can be made.

1. Following an intravenous injection its action begins to take effect within a minute as compared with two minutes for neostigmine.

2. Although Ro 2-3198 is reported to have only one-hundredth the anticholinesterase activity of neostigmine there is no doubt that, in man, subjective symptoms of parasympathetic stimulation occur such as sweating, salivation and intestinal stimulation. It also produces bradycardia. These actions of the drug last a short time, whereas those of neostigmine are sustained. The subjective effect of neostigmine on the bowel may last as long as 45 minutes. This finding with Ro 2–3198 is in accordance with that of Randall, who found that it is comparatively easily washed out of a preparation of the isolated intestine.

3. The short period of action of Ro 2-3198 may lead to recurarization of a patient if its effect wears off before that of the relaxant. Ro 2–3198 is therefore more satisfactory against a relaxant, the effect of which is beginning to wear off, than against a recently injected dose. To our knowledge no case has yet been reported of a return to the curarized state following the use of neostigmine.
4. Clinically Ro 2-3198 is similar in action to neostigmine but lasts a very much shorter time. It is suggested that 20 mg. might be considered equivalent to 2.5 mg. of neostigmine, though the statement of equivalents is misleading unless it is understood to refer only to immediate action rather than long-term.

5. The use of atropine sulphate with Ro 2-3198 is not considered necessary, and in this series has been omitted without ill effect.

DANGERS OF ANTIDOTES

Stimulation of the parasympathetic nervous system produced by neostigmine may cause salivary and bronchial secretion, bronchial constriction and intestinal colic. While these effects are undesirable, it is the slowing of the heart due to vagal stimulation which may endanger life. Vagal stimulation may cause the heart to stop in diastole, though despite continued stimulation it may start again by the operation of the vagal escape phenomenon.

It is well established that an adequate dose of atropine sulphate should be given in conjunction with neostigmine in order to minimize the latter's muscarinic effect. There is, however, a difference of opinion as to whether the atropine sulphate should be given synchronously with neostigmine or whether it should precede the latter. On theoretical grounds it should be given some 15 minutes before neostigmine because its full vagal blocking effect takes longer to develop than the vagal stimulating effect of neostigmine. Goodman and Gilman (1941) point out that as atropine sulphate has a central stimulating effect it may at first produce a slowing of the pulse owing to its
effect on the vagal centres in the brain. It would thus enhance the very effect of neostigmine which it was intended to reduce. However, the fact remains that even with the doses of atropine sulphate normally used clinically, i.e. 1.3 mg.-0.65 mg., 2.5 mg. neostigmine always produces a slowing of the pulse rate. Furthermore, in the conscious subject the intestinal colic was very little mitigated. These facts are not surprising in the light of Goodman and Gilman’s view that doses of 2 mg. are necessary completely to block the vagus in man. Both tubocurarine chloride and gallamine triethiodide block the vagal ganglia and therefore contribute to the protection afforded to the patient by atropine sulphate. It follows that it is less safe to give neostigmine to an uncurarized patient than to a curarized one, and consequently it is essential to ensure that any respiratory depression at the end of an operation is due more to neuromuscular paralysis than to central depression before administering neostigmine.

Patients already under the influence of drugs which produce bradycardia are probably more susceptible to the dangers of neostigmine. Cyclopropane has a direct depressant effect on the conducting tissue of the heart and enhances the effect of neostigmine in producing cardiac arrest and in preventing the operation of the vagal escape phenomenon. Jaundice is associated with bradycardia and it may be more than a coincidence that two of the three recorded deaths associated with neostigmine were in deeply jaundiced patients.

A case described by Macintosh (1949) illustrates the dangers implicit in the use of neostigmine or any vagal-stimulatory drug when the conducting mechanism of the heart is depressed.
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A gravely ill man aged 38 years with a pulse of 140 per minute was to be operated on for a perforated gangrenous appendix. Anaesthesia was with thiopentone and cyclopropane. Relaxation was obtained with d-tubocurarine chloride given intermittently in doses of 15 mg., 10 mg. and 5 mg. At the end of the operation the pulse rate was 100 per minute and the tidal exchange was so inadequate that assisted respiration was necessary. 2.5 mg. of neostigmine with 0.65 mg. of atropine sulphate were injected and the patient died within a few minutes.

Clutton-Brock (1949) also describes a death following neostigmine:

The patient, aged 75 years, was deeply jaundiced and had undergone an operation for relief of common bile duct obstruction. Anaesthesia was by Kemithal 1 gramme, d-tubocurarine chloride 25 mg. in divided doses and 50 per cent nitrous oxide and oxygen. Assisted respiration was maintained throughout the operation. Cyclopropane was given at the end of the operation to afford relaxation for peritoneal suture. Neostigmine 2 mg. with atropine sulphate 0.65 mg. was then injected intravenously. Shortly after this the patient became grey and pulseless and died despite cardiac massage. At necropsy the myocardium was said to be in a very poor condition.

These two cases are examples of the association of neostigmine with death under cyclopropane, and with the possibility of jaundice and myocardial degeneration as contributory factors in the latter.

A third fatality associated with neostigmine given as an antidote to d-tubocurarine chloride has been described by Hill (1949):

The patient, a deeply jaundiced baby of 7 weeks, weighing 6 lb. 7½ oz., underwent an operation for congenital atresia of the common bile duct. Anaesthesia was induced with open drop ether and following this a total of 0.9 mg. d-tubocurarine chloride was given. The operation lasted 1½ hours, relaxation was adequate and respiration and pulse were satisfactory throughout. At the conclusion of the operation the child was given an injection of 0.25 mg. of neostigmine and 0.22 mg. of atropine sulphate intravenously. It collapsed almost immediately and died despite remedial measures.
The dose of neostigmine given, 0.25 mg., would be proportional to a dose of 6 mg. for a 70 kg. adult: a very large dose under any circumstances. While it is probable that sheer overdose was responsible for this child's death one may observe in passing that the child was probably no longer under the influence of the d-tubocurarine chloride and that the contributory protective effect of vagal blockage was therefore no longer present. It is interesting to note also the association of this fatality with jaundice.

Very marked vagus bradycardia may be produced even when the heart is apparently not under the influence of other depressive drugs. This is illustrated by the next case.

A 60-year-old man was operated on for diathermy removal of a carcinomatous polyp of bladder and implantation of radon seeds. He had a blood-pressure of 210/140 mm. of mercury but was fully compensated, leading an active life and complaining only of haematuria. Premedication was with Omnopon 10 mg. and scopolamine 0.43 mg. and anaesthesia with thiopen-tone 0.7 gramme and nitrous oxide-oxygen. Pethidine hydrochloride 25 mg. was added towards the end of the operation and 30 mg. of d-tubocurarine chloride were used to produce relaxation. At the end of operation one hour and ten minutes after induction, the blood-pressure was 160/120 mm. of mercury and the pulse rate 90/minute. He was given neostigmine 2.5 mg. and atropine sulphate 0.65 mg. intravenously. Within ten minutes he developed a marked sinus bradycardia of 40 per minute, a fall in cardiac output so that the systolic pressure was with difficulty recorded at 60 mm. of mercury and Cheyne-Stokes type of respiration. He was cyanosed, cold and sweating but able to open his eyes and respond when asked questions. Respiration reverted to normal when he was put on oxygen and an electrocardiogram taken at this point confirmed the condition of sinus bradycardia with a pulse rate of 44/minute. He was given Methedrine 10 mg. intravenously and 10 mg. subcutaneously. 15 minutes later his pulse rate was 77/minute and blood-pressure 180/120 mm. of mercury. He was fully conscious, talking and co-operative. Postoperative recovery was uneventful.
Neostigmine was given at the termination of operation because there was evidence of residual curarization despite adequate respiration. Atropine sulphate was given with the neostigmine, since pethidine had been given previously. Five minutes after the injection the patient was moving and talking, his blood-pressure was near his pre-operative level, and there was no evidence of parasympathetic stimulation as evidenced by salivation, or bronchial spasm, nor was the pulse rate decreased at this point. Gross sinus bradycardia developed on the way back to the ward and within a further five minutes. It is interesting to note the delay in the onset of the effect, and it is fortunate that during the period of collapse no irreversible change took place in the patient. It would have been preferable to have given the atropine sulphate before the neostigmine, but it is by no means certain that such a dose would have prevented the sinus bradycardia.

Neostigmine may be potentially dangerous in ways other than by the causation of cardiac arrest or extreme bradycardia. In conscious subjects atropine sulphate appeared to have little effect in mitigating the severity of the symptoms of bowel stimulation caused by neostigmine. It is held by some that the bowel, overstimulated by neostigmine given at the end of an operation, may be more prone subsequently to develop post-operative ileus. A case has been brought to our notice in which a colostomy was opened immediately at the end of an operation. Neostigmine was given to abolish the remaining curarization. The colostomy "worked" copiously and the patient died of peritonitis.

A further reason for caution in the use of neostigmine is that the increased bronchial secretion which may occur despite the administration of atropine sulphate may be a
factor in the causation of post-operative pulmonary atelectasis. Bronchospasm in susceptible subjects may also follow an injection of neostigmine.

It follows that neostigmine is a potentially dangerous drug despite the large number of occasions on which it has been used without serious consequences. It would therefore be safer not to regard the standard dose of 2.5 mg. as the minimum effective dose, since in many cases as little as 1 mg. has produced the desired effect. A safer policy would be to give an initial dose of 1 mg., preceded of course by atropine sulphate, followed by increments of 0.5 mg. until the desired effect has been obtained.

DISCUSSION

The introduction into clinical practice of the ultra-short-acting muscle relaxants such as succinyl choline may limit the occasions on which it may be necessary to use neostigmine or other antidotes to curarizing agents. As long as the longer-acting "true" curarizing drugs such as d-tubocurarine chloride or gallamine triethiodide continue to be used, the need for an efficient antidote to their action will remain.

Of the antidotes available neostigmine appears to be the most efficient. Ro 2–3198 has less marked side-actions than neostigmine, but its efficiency, even in very large doses, is limited by its relatively short period of action. American reports suggest that Ro 2–3198 is more effective than neostigmine, but their comparative dose of neostigmine is 0.5 mg., which is very much smaller than the doses usually employed in British practice. A more accurate assessment might be made with electromyographic studies rather than on clinical impressions, but our experience
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has shown differences sufficiently great to be appreciated easily by clinical observation.

If the exact mode of action of Ro 2–3198 were known, it might be possible to use the drug with greater effectiveness. Experimental evidence suggests that it does not act by inhibiting cholinesterase. If we accept this evidence, obtained from animal experiments, another explanation for its mode of action must be sought. The fact that reversion to the curarized state can occur in man shows that Ro 2–3198 does not free the curarizing drug from its attachment to the muscle end-plate. In view of its slight but definite parasympathetic stimulant action it would appear that it exerts its antidotal effect by means of a non-specific cholinergic activity.

The search for a specific antagonist to the curarizing agents continues. So far it does not appear that a drug has yet been discovered which will detach curare from the muscle end-plate. The known antagonists appear merely to increase the degree of stimulation at the neuromuscular junction and reversion to the curarized state will occur if the period of action of the antagonist is shorter than that of the curarizing drug. There is no evidence that the known antagonists increase the rate of elimination of the curarizing agents.

SUMMARY

The indications for the use of antidotes to muscle relaxants are enumerated.

The pharmacology of a new drug, Ro 2–3198 (Tensilon), is discussed.

The effects of neostigmine and Ro 2–3198 (Tensilon) on the conscious subject and on patients under anaesthesia are recorded.
The dangers of neostigmine are discussed with reference to known mishaps which have occurred following the use of the drug.

We are indebted to Roche Products Ltd. for generous supplies of Ro 2-3198 (Tensilon) on which part of the subject matter of this paper is based.

REFERENCES