TENSILON: A NEW ANTI-CURARE AGENT

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While it is true that antidotes to the curarizing drugs are regarded with suspicion in some quarters, there is no doubt that most anaesthetists would not like to be without an agent of this type permanently. The currently available drug is "Prostigmin" (neostigmine B.P.) which when given in adequate dose and with sufficient atropine will produce permanent reversal of the muscle-paralysing action of the d-tubocurarine and other like substances. There have, however, been reports of cases in which it seemed possible, though it was by no means certain, that the muscarinic action of the neostigmine might have been responsible for fatalities (Macintosh, 1949; Clutton-Brock, 1949).

When, therefore, the drug Tensilon became available and appeared to be comparatively free from such dangers it seemed as if there was no longer any need to subject patients to the possible risk that the quantity of atropine given with the neostigmine might not be sufficient to control unwanted side-effects.

Tensilon (3 hydroxy-phenyl dimethyl ethyl ammonium bromide) was selected by Randall (1950) from a group of related compounds as that possessing the greatest anti-curare activity and the least marked muscarinic effect. Its action was examined in detail by Riker et al. (1949), Wescoe et al. (1949, 1950), Artusio et al. (1950), Riker and Wescoe (1950), and others. It was shown to be effective in reversing the muscle-paralysing action of d-tubocurarine, both in experimental animals and in man. It also, in twenty
times the de-curarizing dose, could itself produce a myoneural block similar to that induced by decamethonium. It possessed little anticholinesterase activity but did have a mild depressor action on the dog, probably as a result of its chemical similarity to acetylcholine. Its depressor action was converted to a mild pressor action by atropine. In man its action on the blood-pressure and pulse rate was comparatively slight. It thus seemed as if it would prove the ideal decurarizing agent. An extended investigation of its effects in patients curarized with di-methyl tubocurarine and gallamine triethiodide was therefore desirable. No attempt was made to use it as an antidote to decamethonium as Randall (1951) had already found it to be useless in this respect.

The first step in the investigation was obviously to make certain in the laboratory that Tensilon was as effective as an antidote to gallamine triethiodide as it was to d-tubocurarine. Since the reason for giving decurarizing drugs in the human subject is to restore respiration, the effect of Tensilon on the breathing of curarized cats and dogs under pentobarbitone anaesthesia was studied. It was found that the drug would reverse both complete apnoea and respiratory depression due to gallamine triethiodide. Further, the diaphragmatic and intercostal components of respiration recovered together as they do when neostigmine is given. The effect of Tensilon on the blood-pressure of the cat was similar to that noticed by Riker and his colleagues (1949) in their experiments. When the drug was given alone there was sometimes a small evanescent fall in blood-pressure. When it was given with atropine there was a temporary slight rise in blood-pressure. This brief investigation seemed to indicate that Tensilon would be as effective against curarization due to gallamine triethiodide as it was against
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that due to d-tubocurarine. In view of the close chemical similarity between this latter drug and its di-methiodide it scarcely seemed necessary to confirm the effectiveness of Tensilon as an antidote to the latter drug in the laboratory. Tensilon was, however, tested as a decurarizing agent against Win 2747 (Hoppe, 1950) in the laboratory and it was found to be ineffective.

DECURARIZING ACTION OF TENSILON IN MAN

Methods. The decurarizing action of Tensilon was studied in 55 patients; 17 of these were curarized with d-tubocurarine, 8 with di-methyl tubocurarine, and 30 with gallamine triethiodide (Flaxedil). The numbers of cases in these groups do not give an adequate indication of the depth of curarization involved, but in table I will be found the doses of these drugs used by the author in a previous series of abdominal operations where an attempt was being made to estimate the equivalent doses of curarizing agents; wherever it was necessary an additional dose of relaxant was given to facilitate closure of the abdomen.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage up to 30 mins. (mg.)</th>
<th>Dosage 31-60 mins. (mg.)</th>
<th>Dosage 61+ mins. (mg.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>d-tubocurarine</td>
<td>16 (10—30)</td>
<td>26 (15—45)</td>
<td>34 (20—50)</td>
</tr>
<tr>
<td>dimethyl tubocurarine</td>
<td>9 (6—11)</td>
<td>11 (4—18)</td>
<td>19 (8—33)</td>
</tr>
<tr>
<td>gallamine triethiodide</td>
<td>84 (60—100)</td>
<td>111 (80—160)</td>
<td>160 (90—240)</td>
</tr>
</tbody>
</table>

The figures in parenthesis indicate the range of dosage in each group. The mean number of cases on which each of these observations are based is 14.2 and the range 4—26.
All cases were anesthetized with nitrous oxide and oxygen after a barbiturate induction. Supplementary analgesic drugs were given where necessary, with the result that most of the patients recovered consciousness very promptly when the anesthetic was stopped. It was thus very often possible to test the degree of recovery from the curarizing drug by the ability of the patient to open his eyes in response to a command, or by his pulling a face when his supraorbital nerve was compressed. Return of the lid reflex was also sought, though it was not invariably present, even in patients who could speak. The quality of the spoken word was observed and the disappearance of the thick speech of partial curarization regarded as further evidence of complete recovery. Even before the patient had recovered so completely it was often possible to tell whether decurarization was complete. Thus the abolition of chin tugging and the return of full intercostal respiratory movement gave a fairly reliable guide. The restoration of completely effective coughing in response to movement of the endotracheal tube was also fairly conclusive evidence of complete decurarization, as was the appearance of rigidity of the abdominal wall as the patient strained on his tube. On the basis of these criteria it was possible to sort out the results obtained into cases of complete decurarization, cases of partial decurarization, and failures.

At first it was accepted, mainly on the basis of the experience of the case described in the section on side-effects, that the maximum safe dose of the drug was 10 mg. Later, however, it was found possible, with suitable modification of the dose of atropine, to increase the dose of Tensilon to 20 mg, with complete safety. This dose, however, was usually given in two fractions of 10 mg., or even three fractions of 10, 5 and 5 mg., rather than all at once. A child of 9 years of age
whose weight was 4 stones received her Tensilon in doses of 5, 2.5, and 2.5 mg. Atropine was dissolved in the Tensilon and given simultaneously with each dose so that not more than 1/100 gr. (0.65 mg.) of this drug was administered to any single patient.

**Results.** The results obtained are set out in the appended tables II, III and IV. It will at once be apparent that even in doses of 20 mg. Tensilon is not a decurarizing agent of reliability comparable to that of neostigmine bromide.

**TABLE II**

*The Effectiveness of Different Doses of Tensilon.*

<table>
<thead>
<tr>
<th>Dose of Tensilon (mg.)</th>
<th>Degree of Decurarization after Tensilon</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>27</td>
</tr>
<tr>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>20</td>
<td>12</td>
</tr>
</tbody>
</table>

There were too many cases in which its effect was incomplete. This incompleteness had several interesting associations. Thus the drug was most effective where the curarization was mild and had already decreased to the stage of slight respiratory depression. It was very unreliable in patients whose spontaneous respiratory activity had been nearly abolished (table III) by the curarizing agent. Tensilon too seemed to be a more satisfactory decurarizing drug

**TABLE III**

*The Effectiveness of Tensilon as an Antidote at Various Depths of Curarization.*

<table>
<thead>
<tr>
<th>Degree of Curarization before Tensilon</th>
<th>Degree of Decurarization after Tensilon</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete</td>
</tr>
<tr>
<td>Deep</td>
<td>5</td>
</tr>
<tr>
<td>Moderate</td>
<td>19</td>
</tr>
<tr>
<td>Mild</td>
<td>16</td>
</tr>
</tbody>
</table>
in cases to whom the relatively short acting drugs, gallamine triethiodide and dimethyl tubocurarine, had been given and to be less valuable in producing permanent reversal of the rather longer acting d-tubocurarine (table IV). There was another interesting feature of the action of Tensilon in that

**TABLE IV**

*The Effectiveness of Tensilon as an Antidote to Various Curarizing Agents.*

<table>
<thead>
<tr>
<th>Curarizing Agent</th>
<th>Degree of Decurarization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete</td>
</tr>
<tr>
<td>d-Tubocurarine</td>
<td>11</td>
</tr>
<tr>
<td>Dimethyl Tubocurarine</td>
<td>7</td>
</tr>
<tr>
<td>Gallamine Triethiodide</td>
<td>26</td>
</tr>
</tbody>
</table>

very often more or less complete decurarization followed the administration of the first dose of the drug and then a relapse into partial curarization occurred. This relapse could be reversed by a second dose, but in some cases a third dose was required before permanent and complete decurari-

zation was produced. The interval between these successive doses was often such that there was some doubt as to whether the degree of recovery finally obtained was not due in part at least to spontaneous elimination of the curarizing drug.

**Side-effects.** Since Tensilon had a close chemical similarity to acetylcholine and neostigmine it seemed advisable to give atropine with it. When this was done the blood-pressure changes which occurred were small (table V). Further, they nearly always righted themselves spontaneously in a few minutes. Indeed the only case in which anxiety was caused by the hypotensive action of Tensilon was a woman in whom 10 mg. given with 1/100 grain (0.65 mg.) of atropine had failed to produce adequate decurarization.
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TABLE V
The Blood-pressure Changes caused by Tensilon given with Atropine.

<table>
<thead>
<tr>
<th>Blood-pressure Changes</th>
<th>Rise</th>
<th>Nil</th>
<th>Fall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Cases</td>
<td>3</td>
<td>8</td>
<td>26</td>
</tr>
<tr>
<td>Mean change (mm. Hg.)</td>
<td>16</td>
<td>—</td>
<td>15.8 ± 8.1 (Range 5-30)</td>
</tr>
</tbody>
</table>

A second 10 mg. was given, in this case without additional atropine, and the blood-pressure fell from 105 mm. to 70 mm. Hg in two minutes. A second 1/100 grain (0.65 mg.) of atropine with 10 mg. of Methedrine were then given and the blood-pressure level was restored to 90 mm. Hg, though only at the expense of producing a severe tachycardia. Subsequent experience indicated that the administration of a total dose of atropine of 1/100 grain (0.65 mg.) was sufficient to prevent major blood-pressure changes and since this policy has been adopted side-effects have been minimal.

The changes in the pulse rate have been of equally little significance. The general tendency was for the pulse rate to settle at a level of about 100 per minute. Thus in cases where the pulse had already been accelerated by gallamine triethiodide there was a tendency to slowing, and where the pulse rate was already slow in cases to whom d-tubocurarine or its di-methiodide had been given there was an acceleration. The actual figures for the cases for which the information is available are: pulse rate unchanged 6 cases; pulse rate slowed 16 cases; pulse rate accelerated 15 cases.

The changes in pulse rate after the administration of Tensilon with atropine differ markedly from those produced by neostigmine and atropine (figs. 1 and 2). When this latter combination of drugs is given there is always an
initial cardioacceleration, most marked when 1/50 grain (1.3 mg.) is the dose of atropine. This is followed by a slowing of the pulse rate. The bradycardia is never extreme when this dose of atropine is used, but may be alarming if only 1/100 grain (0.65 mg.) of atropine is given. When Tensilon is given with 1/100 grain (0.65 mg.) of atropine the bradycardia does not occur. The pulse rate settles almost immediately at about 100 per minute and no further change appears.

**Spirometric Studies.** The use of the respiratory depression as a measure of curarization is open to criticism, on the ground that it is possible for diaphragmatic over-action
to compensate for the loss of ventilation produced by intercostal paralysis. None the less Artusio and his colleagues (1950) used this criterion in his study of the action of Tensilon and some related substances. It therefore seemed as if it might be worth while to repeat some of his investigations. For this purpose patients were connected to a closed-circuit apparatus through which only a basal flow of oxygen was running. On the expiratory side of the circuit there was inserted a wet gas meter, and with the aid of this the patients' ventilation per minute was measured. These studies added nothing to the evidence of decurarization
obtained from clinical observations reported above, particu-
larly as they could be applied only to patients whose 
breathing was already forcible enough to ensure that serious 
anoxia would not occur during the period of measurement. 
The results are shown graphically in figure 3 and do give 
numerical confirmation of the fact that the decurarization 
produced by Tensilon is maximal immediately after its 
administration; thereafter in some cases curarization tends 
to return, but the same degree of recovery can be produced 
by a second dose of Tensilon.

DISCUSSION

The most immediate conclusion to be drawn from this 
study is that Tensilon is not a completely satisfactory 
decurarizing agent in man in that the effect of a single dose 
tends to wane shortly after its administration. Adequate 
decurarization can probably be produced by a series of 
doses of the drug, but as there is already a completely satis-
factory single-dose antidote to curarization in neostigmine 
bromide there would seem to be little justification for the 
use of Tensilon on this ground. The case for the employ-
ment of Tensilon rests on the relative absence of side-effects 
after its administration. If it is considered that the secondary 
bradycardia which appears in cases to whom neostigmine 
bromide has been given is an indication that complete 
cardiac inhibition will one day occur in a patient with pro-
nounced vagal tone, then Tensilon is the preferable 
decurarizing agent. If, however, it is believed that 1/50 
grain (1.3 mg.) of atropine affords adequate protection 
against the muscarinic activity of neostigmine, then this 
more certain antidote will obviously be the anaesthetist's 
choice for the curarized patient.

No very direct evidence concerning the mode of action of
Tensilon has emerged from this study, but its findings are readily explained in terms of what is already known about its action. It has been demonstrated electronically that Tensilon converts each successive muscle response to a nerve impulse, from a single twitch to a short tetanus. This action is not peculiar to Tensilon but is shared by eserine and neostigmine. There is, however, an important difference between Tensilon and the other drugs. The anticholinesterases produce their repetitive action by interfering with hydrolysis of acetylcholine produced at the nerve ending, with the result that there is still an effective concentration of this substance at the myoneural junction at the end of the refractory period of the muscle fibre. Tensilon on the other hand has a relatively insignificant anticholinesterase activity (Cohen and Unna, 1951) and produces its anti-curare effect by causing an increase in the sensitivity of the muscle fibre to normal amounts of acetylcholine. It is of interest that this stimulant effect on muscle contraction is not confined to curarized muscle. When injected into normal patients Tensilon temporarily increases the force of muscle contraction and may cause muscular fasciculation and result in deviation of the eyes into abnormal positions (Westerberg et al., 1952). On the other hand because the drug possesses only slight anticholinesterase activity its action on the circulatory system tends to be immediate and short acting. Further, there is none of the secondary muscarinic activity which characterizes the action of neostigmine.

The final conclusion would seem to be that neither neostigmine nor Tensilon is the perfect decurarizing agent. The former gives rise to unwanted muscarinic effects which require for their control the administration of large doses of atropine, and the latter drug is too evanescent in its action...
to be of much use in single doses, though it seems to be possible that multiple injections may prove to be relatively satisfactory. Tensilon may, however, point the way to the synthesis of the perfect anti-curare agent by indicating that this might well be a drug of similar structure which is less readily inactivated in the body.

SUMMARY

The anti-curare action of Tensilon (3 hydroxy-phenyl dimethyl ethyl ammonium bromide) has been investigated. It was found that the effect of this drug, though apparently complete and permanent in experimental animals, was somewhat evanescent in man. If complete decurarization was to be maintained in the human subject it was often necessary to give second or even third doses of Tensilon. Circulatory side-effects were slight when atropine was given with Tensilon. The conclusion is drawn that Tensilon, though free from the more serious muscarinic actions of neostigmine, is not as reliable an antidote to the muscle paralysing action of d-tubocurarine.

REFERENCES