ANTAGONISM OF BLOCKADE PRODUCED BY
ATRACURIUM OR VECURONIUM WITH
LOW DOSES OF NEOSTIGMINE

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The action of atracurium and vecuronium can be reversed readily by neostigmine 2.5 mg even when the degree of residual neuromuscular block-ade is considerable [1,2]. Thus, using the compound action potential of the electromyograph, Fox, Keens and Utting [1] showed that neostigmine 2.5 mg produced rapid reversal of residual atracurium blockade if given when the recovery of the first response of the train-of-four (TOF) stimuli (A') was only 10% of control (A) and that there was no advantage in using neostigmine 5 mg at this degree of block. Using an identical procedure, Jones, Hunter and Utting [2] reported similar results with vecuronium, again finding recovery to be as rapid with a dose of neostigmine 2.5 mg as with 5.0 mg. The results from these two studies suggested that doses of neostigmine less than 2.5 mg might be clinically effective. We have studied, therefore, the efficacy of neostigmine 1.25 mg and 0.625 mg in the antagonism of block produced by atracurium or vecuronium, in an attempt to assess if these lower doses of anticholinesterase were sufficient to produce prompt recovery.

PATIENTS AND METHODS

Permission for the study was granted by the hospital Ethics Committee and informed consent was obtained from each patient. Forty-five patients (table I) were investigated; all were healthy and were scheduled to undergo general surgical or gynaecological procedures. They were allocated to four groups. Patients in group I (n = 11) received atracurium and were given neostigmine 0.625 mg to antagonize blockade; group II (n = 13) received atracurium and neostigmine 1.25 mg; group III (n = 10) received vecuronium and were given neostigmine 0.625 mg to ant- agonize blockade and group IV (n = 11) received vecuronium and neostigmine 1.25 mg.

The initial dose of atracurium was 0.5 mg kg⁻¹ and of vecuronium 0.1 mg kg⁻¹; up to two increments, of 0.2 mg kg⁻¹ or 0.04 mg kg⁻¹, respectively, were given if the ratio A'/A recovered to 10% during surgery. The anticholinesterase...
was also given when A'/A was 10%. Atropine 0.6 mg was administered with the neostigmine.

All patients were premedicated with promethazine 50 mg by mouth the night before surgery, followed either by diazepam 10 mg by mouth 2 h before operation or by morphine 10 mg with cyclizine 50 mg (Cyclimorph) i.m. 1 h before operation.

The anaesthetic technique and methods used were identical to those reported in detail previously [1,2]. Anaesthesia was induced with thiopentone, fentanyl and droperidol and the patient breathed 70% nitrous oxide in oxygen via a Magill circuit. No other inhalation agent was used. Ventilation was assisted if necessary and normocapnia maintained with the aid of a Normocap (Datex). A control recording of the electromyograph (EMG) was obtained using the Medelec MS6 electromyograph. Train-of-four (TOF) supramaximal stimuli (0.2 ms; 2 Hz) were delivered to the ulnar nerve at 12-s intervals and a control compound muscle action potential (CMAP) recorded, at least 10 responses being obtained. The initial dose of the myoneural blocker was given and the trachea intubated when it was thought to be clinically appropriate. TOF monitoring continued at 1-min intervals throughout the study.

At the end of surgery and when A'/A had returned to 10%, TOF monitoring was returned to 12-s intervals and the appropriate dose of neostigmine accompanied by atropine 0.6 mg was given. The times taken for A'/A and D'/A' (TOF ratio: ratio of fourth response to first) to reach 70% were measured and the height of A'/A when D'/A' had reached 70% noted. Some time after this (5-15 min) anaesthesia and monitoring were discontinued and the patient allowed to recover from anaesthesia whilst breathing oxygen.

### RESULTS

#### Atracurium

The mean times to 70% recovery of A'/A and D'/A' in groups I (receiving neostigmine 0.625 mg) and II (neostigmine 1.25 mg) were compared with each other and with previous results [1] from patients who received neostigmine 2.5 mg, neostigmine 5.0 mg or no neostigmine (spontaneous recovery) (table II).

Each dose of neostigmine significantly shortened the period of recovery of both A'/A and D'/A' to 70% compared with the group in which spontaneous recovery was studied. Neostigmine 2.5 mg and 5.0 mg produced significantly more rapid recovery than neostigmine 0.625 mg, but there was no significant difference between the rate of recovery after neostigmine 2.5 mg compared with neostigmine 2.5 mg or 5.0 mg, or between neostigmine 0.625 mg and 1.25 mg.

The mean height of A'/A in group I at the completion of monitoring, when D'/A' was 70% was 94.1% (range 82-100%) and in group II was 92.3% (range 77-100%).

#### Vecuronium

The mean times for 70% recovery of A'/A and D'/A' in group III (receiving neostigmine 0.625 mg) and group IV (neostigmine 1.25 mg) were compared with each other and with previous results from patients who received neostigmine 2.5 mg, neostigmine 5.0 mg or no neostigmine (spontaneous recovery) (table III).

When the results from patients receiving neostigmine 0.625 mg are compared with those in whom spontaneous recovery was allowed, it can be seen that recovery of A'/A, but not D'/A', was significantly more rapid. In contrast, neostigmine 2.5 mg, 2.5 mg or 5.0 mg significantly increased the rate of recovery of both variables compared
TABLE II. Mean (SD) times to 70% recovery from block by atracurium after neostigmine 0.625 mg or 1.25 mg (groups I and II) compared also with results previously reported [1] for neostigmine 2.5 mg and 5.0 mg and for spontaneous recovery. Statistical significance: comparing each dose of neostigmine with spontaneous recovery—** P < 0.01; *** P < 0.001; between the smallest dose of neostigmine (0.625 mg) and the three larger doses (1.25 mg, 2.5 mg and 5.0 mg)—† P < 0.05

<table>
<thead>
<tr>
<th>Dose of neostigmine (mg)</th>
<th>Group I</th>
<th>Group II</th>
<th>ref. [1]</th>
<th>ref. [1]</th>
<th>Spontaneous recovery</th>
</tr>
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<tbody>
<tr>
<td>0.625</td>
<td>11</td>
<td>13</td>
<td>10</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>1.25</td>
<td>13.0**</td>
<td>9.9***</td>
<td>8.2****†</td>
<td>7.4***†</td>
<td>25.0</td>
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<td></td>
<td>(4.3)</td>
<td>(4.7)</td>
<td>(2.9)</td>
<td>(1.7)</td>
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<tr>
<td>2.5</td>
<td>19.3**</td>
<td>14.2**</td>
<td>12.0****†</td>
<td>11.2***‡</td>
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<td>(5.6)</td>
<td>(6.9)</td>
<td>(3.5)</td>
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with spontaneous and with neostigmine 0.625 mg. However, there was no significant difference between the rate of recovery of A'/A or D'/A' in the group who received neostigmine 1.25 mg compared with neostigmine 2.5 mg or 5.0 mg.

The mean height of A'/A in group III on completion of monitoring was 91.1% (range 81.5–100%) and in group IV was 92.0% (range 83–97%).

DISCUSSION

Neostigmine 1.25 mg was nearly as rapid at antagonizing a considerable degree of residual block produced by both atracurium or vecuronium, as was neostigmine 5.0 mg or 2.5 mg; although the mean times to 70% recovery of D'/A' after vecuronium were certainly longer after neostigmine 1.25 mg than neostigmine 5 mg it is doubtful if this is clinically important.

With the smallest dose of neostigmine (0.625 mg) the situation was different. For atracurium, there was a significant difference in the times at which 70% recovery was reached when compared with spontaneous recovery; in other words the small dose of neostigmine accelerated recovery. However, recovery was slower than with neostigmine 2.5 mg (and 5.0 mg) and, as it took a mean time of 19 min for D'/A' (perhaps the best criterion of recovery) to reach 70%, it might be considered clinically unacceptable.

When neostigmine 0.625 mg was administered to those who had received vecuronium, the time to 70% recovery of D'/A' was not different from the mean time when recovery was spontaneous, but was different from the larger doses, including
neostigmine 1.25 mg; the time for A'/A to reach 70% was also longer than with the other doses, although shorter than when recovery was spontaneous.

Clinical deductions from these data are likely to be controversial. If there is a considerable degree of residual block following both blocking drugs (for instance, only the first twitch of the TOF present) neostigmine 2.5 mg might be considered a suitable dose to antagonize this. Neostigmine 1.25 mg should be adequate for both blockers if it be appreciated that antagonism to a safe degree of block would be slower in some patients. Even neostigmine 0.625 mg might be adequate follow-
ing atracurium, although it must be emphasized that it took more than 19 min in this study for D'/A' to reach 70% after this dose. Certainly little acceleration of recovery of D'/A' after vecuronium may be produced with neostigmine 0.625 mg. In this respect the difference between the two drugs is related probably to more rapid spontaneous recovery from vecuronium than from atracurium. It should be noted that recovery might be even more prolonged if a volatile agent is used.

In this study a maximum of two increments of atracurium or vecuronium was given. Although atracurium is not thought to cumulate [3], it has been suggested that vecuronium may do so, especially after several increments [4]. If this is the case, smaller doses of neostigmine may be insufficient to produce adequate recovery from the residual block produced after several increments of vecuronium; thus it is possible that the number of increments of a neuromuscular blocking agent used may affect the dose of neostigmine which should be given. However, Miller, Larson and Way [5] demonstrated that the amount of neostigmine required to antagonize a profound block (5% recovery of control twitch height) produced by tubocurarine, gallamine or pancu-
ronium was unrelated to the amount of blocker given. Using repeated boluses of neostigmine 0.25 mg every 3 min, commencing when the twitch height had recovered to 5% of control, these workers also found that little more than neostigmine 1 mg was required to produce 80% recovery of the twitch height after pancuronium and tubocurarine, although more than 2 mg was required if gallamine had been given.

Attempts have also been made to antagonize residual block produced by atracurium using divided doses of neostigmine (0.01 mg kg\(^{-1}\) follow-
ed, 3 min later, by 0.04 mg kg\(^{-1}\)) and the results compared with a single bolus dose of neostigmine 0.05 mg kg\(^{-1}\) [6]. Abdulatif and Naguib [6] ad-
ministered the first dose of neostigmine when A'/A was 10%, as in this study, and found a more rapid recovery of D'/A to 75% when neostigmine was given in divided doses. These workers reported that, 3 min after the initial smaller dose of neostigmine (0.01 mg kg\(^{-1}\)) and immediately before the second dose was given, A'/A had reached a mean of 44%—an even faster rate of recovery than that found in this study for a comparable dose of neostigmine (0.625 mg).

The apparently effective use of a smaller dose of neostigmine to antagonize profound neuro-
muscular block is an interesting contrast to the inconsistent effects reported after the use of the shorter acting anticholinesterase, edrophonium, even in large doses. Caldwell, Robertson and Baird [7] demonstrated that, although the onset of action of edrophonium 0.8 mg kg\(^{-1}\) was faster than neostigmine 0.07 mg kg\(^{-1}\) when used to antagonize both atracurium and vecuronium, edrophonium did not produce as fast a clinical recovery. Indeed, when edrophonium was used after vecuronium, recovery was more variable than after atracurium and was considered, on occasions, to be delayed unacceptably. These results have been substantiated by other workers for both vecuronium [8] and atracurium [9]. The inconsistent effects of edrophonium, even in larger doses, contrast markedly with the results reported in this study.

Even with low doses neostigmine would seem to be a more reliable anticholinesterase than edrophonium. In addition, it would seem preferable to use neostigmine, even in low doses, than to allow spontaneous recovery to occur, especially if neuromuscular monitoring is not used. We would suggest that the concept that anti-
cholinesterases are not required if atracurium or vecuronium are used should be viewed with caution.

ACKNOWLEDGEMENT

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REFERENCES


