ANTAGONISM OF MODERATE DEGREES OF VECURONIUM-INDUCED NEUROMUSCULAR BLOCK BY SMALL DOSES OF NEOSTIGMINE

R. A. JOHNSON AND N. J. N. HARPER

Neostigmine is used widely to antagonize non-depolarizing neuromuscular block. In the presence of at least 5% recovery of the single twitch, a dose of 2.5–5 mg has been found adequate for all currently used neuromuscular blocking agents, including vecuronium [1–4]. The main characteristics of this drug are a short duration of action and rapid spontaneous recovery [1, 5–7]. Antagonism is more rapid after pronounced spontaneous recovery has occurred [4, 8] and it has been suggested that a smaller dose of neostigmine might be adequate [9] or that it might be omitted [10]. The use of a smaller dose of neostigmine might reduce the incidence of side effects [11].

Antagonists of neuromuscular blockade have differential effects on the recovery of train-of-four (TOF) fade and on the single response [12–14]. Dose-dependent differences in receptor affinity may influence the TOF ratio. In addition to investigating the recovery of the first response of the TOF, we have also studied the effect of small doses of neostigmine on the TOF ratio.

PATIENTS AND METHODS

We studied 26 patients undergoing gynaecological surgery after Ethics Committee approval and after informed written consent was given by each patient. They were allocated randomly to six groups (A–F) according to the dose of neostigmine to be given. Patients of ASA grades III–V and those suffering from neuromuscular disease were excluded.

SUMMARY

We have studied the influence of a reduced dose of neostigmine on recovery from vecuronium-induced neuromuscular block in 26 adult patients, using electromyographic responses to train-of-four (TOF) stimulation. Neostigmine 10, 20 or 40 μg kg⁻¹ was administered when the first response had recovered spontaneously to 5–10% or 40–50% of control. Antagonism was accepted as adequate when the first response reached 90% of control and the TOF ratio reached 0.7. At both degrees of spontaneous recovery, neostigmine 40 μg kg⁻¹ evoked the most rapid antagonism. Clinical recovery was satisfactory with no differences between groups. Block produced by neostigmine was not observed. The pattern of recovery of the single response and the TOF ratio was not altered by neostigmine in the range of doses studied. We suggest that the dose of neostigmine should not be reduced below 40 μg kg⁻¹, even when all responses of the TOF are present.

Monitoring of neuromuscular function

Control values were established for clinical measures of muscle strength before induction of anaesthesia. In the postoperative period the ability to lift the head clear of the pillow for 5 s and the presence or absence of diplopia were noted. Grip strength was measured by recording the pressure generated in a 50-ml syringe containing 15 ml of air by adduction of the thumb against the plunger. Extraocular muscle weakness was assessed with the Maddox Wing [15].

The ulnar nerve was stimulated supra-maximally at the wrist via silver-silver chloride electrodes with a TOF impulses of 0.2 ms dura-
tion at 2 Hz every 20 s. A Relaxograph (Datex) was used to measure and record the integrated evoked compound electromyogram (ECAP) using similar electrodes placed over the adductor pollicis. The ratios of the first ECAP response to the control (T1:T0) and the fourth response to the first in the same train (T4:T1) were recorded.

Anaesthesia and antagonism of neuromuscular block

One hour after premedication with diazepam 10 mg and droperidol 5 mg by mouth, anaesthesia was induced with fentanyl 2-3 µg kg\(^{-1}\) and thiopentone 3-5 mg kg\(^{-1}\). Anaesthesia was maintained with 70% nitrous oxide and 0.5-2% enflurane in oxygen. Ventilation was controlled to produce normocapnia. The control neuromuscular response was recorded and vecuronium 80 µg kg\(^{-1}\) given as a bolus. A continuous infusion of vecuronium via a separate cannula was used to maintain 90-95% depression of the single response. Normothermia was maintained and arterial pressure and ECG were monitored.

Residual neuromuscular block was antagonized at the completion of surgery. Atropine was given in a dose of 0.4 mg per 1 mg of neostigmine. In groups A, B and C the degree of spontaneous recovery was noted (T1:T0 = 0.05-0.1), the vecuronium infusion discontinued and the antagonist given immediately (10, 20 or 40 µg kg\(^{-1}\), respectively). In groups D, E and F spontaneous recovery was allowed to proceed until T1:T0 = 0.4-0.5, at which point the antagonist was given (10, 20 or 40 µg kg\(^{-1}\)). Recovery of neuromuscular function was regarded as adequate when T1:T0 and T4:T1 were consistently greater than 0.9 and 0.7, respectively, at which time anaesthesia and monitoring were discontinued. Supplementary neostigmine 40 µg kg\(^{-1}\) was administered if recovery was inadequate after 15 min. Patients were observed in a recovery area for 2 h after operation, and residual neuromuscular block was assessed clinically 30, 60 and 120 min after TOF recovery.

Differences in patient characteristics were assessed with Student's t test. The recovery time data were skewed positively and logarithmic transformation was performed. The statistical significance of differences in recovery time between groups was assessed with Wilcoxon's ranked sum test. \(P < 0.05\) was accepted as being significant.

RESULTS

There was no difference between the groups with regard to age, weight or total dose of vecuronium. The degree of spontaneous recovery at which neostigmine was given was within the specified range in groups A–C and D–F (table I).

All patients, including those who needed a supplementary dose of neostigmine, fulfilled our criteria of satisfactory neuromuscular function at the end of the study. There was no clinical evidence of weakness in any patient after the return of consciousness.

Antagonism at minimal spontaneous recovery

When antagonism was attempted at the greater degree of block (T1:T0 = 0.05-0.1, one or two twitches of the TOF present) recovery to T1:T0 = 0.9 was more rapid in group C (the highest dose of neostigmine) than in groups A (\(P < 0.01\)) or B (\(P < 0.05\)) (fig. 1). Recovery of T4:T1 to 0.7 was also more rapid in group C than in the other groups (\(P < 0.05\)) (fig. 2).

Antagonism when moderate spontaneous recovery had occurred

A similar pattern was observed when neostigmine was administered after a greater degree of spontaneous recovery was permitted (T1:T0 = 0.4-0.5). All patients exhibited four responses

<table>
<thead>
<tr>
<th>Table I. Patient characteristics (mean (SD))</th>
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<tr>
<td>Group</td>
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<tr>
<td>-------</td>
</tr>
<tr>
<td>A</td>
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<tr>
<td>B</td>
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<td>C</td>
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Antagonism of neuromuscular block was inadequate in four patients in group A and one patient in each of groups B and D after a single dose of neostigmine. Additional neostigmine 40 μg kg⁻¹ accelerated recovery in all patients and the subsequent rate of recovery was similar to that found after a single dose of 40 μg kg⁻¹ (group F).

Patterns of T1 and TOF recovery

There was no evidence of different patterns of TOF recovery after the different doses of neostigmine, irrespective of the degree of recovery at which it was administered.

Additional neostigmine

Antagonism of neuromuscular blockade was inadequate in four patients in group A and one patient in each of groups B and D after a single dose of neostigmine. Additional neostigmine 40 μg kg⁻¹ accelerated recovery in all patients and the subsequent rate of recovery was similar to that found after a single dose of 40 μg kg⁻¹ (group F).
Clinical assessment of recovery

Twenty-five of the 26 patients were able to co-operate with the clinical assessments. All 25 could maintain a 5-s headlift. Two patients (from groups B and C) experienced diplopia early in the recovery period.

Twenty-three patients were able to perform the grip strength test. In all groups there was a reduction in strength of up to 20% at 30, 60 and 120 min after recovery of the TOF ratio to 0.7. There was marked individual variation and we were unable to demonstrate a significant change in strength with time, or a significant difference between the groups.

Only 11 patients were able to perform the Maddox Wing test after anaesthesia. Exophoria (ocular divergence) of up to 16 dioptres was found. We did not find differences with time or between groups.

DISCUSSION

This study was intended to simulate closely the clinical situation. We used an anaesthetic vapour to obviate awareness and chose enflurane because many of our patients had previously undergone anaesthesia, notwithstanding its well-recognized potentiating effect on non-depolarizing blocking drugs [16].

The rate of recovery from neuromuscular block may be influenced by the mode of administration of the agent. The spontaneous recovery index (time from T1:T0 = 0.25 to T1:T0 = 0.75) is longer after an infusion of vecuronium compared with administration of the same total dose as a series of boluses [17]. It is, therefore, possible that evoked recovery would be more rapid after bolus administration of vecuronium. In order to achieve a steady plasma concentration, vecuronium was given by continuous infusion. Maintenance of T1:T0 at 40-50% of control throughout the surgical procedure was considered to be inappropriate on clinical grounds. Therefore, in groups D–F neostigmine was given when this level of recovery had occurred spontaneously from the steady state of 90–95% block.

Recovery may be influenced by the total dose of myoneural blocker given during the surgical procedure [2, 17]. Our findings may not be applicable directly when larger total doses are given over a prolonged period.

TOF measurements were supplemented by clinical assessments of recovery for two reasons. First, a small dose of neostigmine exhibits a shorter duration of action than conventional doses [18, 19] and there may have been a risk of recurarization. This could not be excluded by electromyography because supramaximal nerve stimulation in the awake patient is painful. Second, a comparison of the different clinical measurements of residual block was thought to be useful. We were unable to demonstrate significant differences in clinical recovery between the groups, in contrast to previous studies in which residual block persisted for several hours [15, 20].

Recovery from the greater degree of block was slow, even when neostigmine 40 µg kg\(^{-1}\) had been given. Smaller doses of neostigmine produced much slower antagonism. In group A (10 µg kg\(^{-1}\)) the mean rate of recovery was no faster than that reported during spontaneous recovery [7], and we suggest that these small doses are inadequate. Recovery was also slow after neostigmine 10 µg kg\(^{-1}\) when a moderate degree of spontaneous recovery had occurred (group D), and one patient required supplementary neostigmine.

The differences in mean recovery times after neostigmine 20 and 40 µg kg\(^{-1}\) were comparatively small. However, there was considerably more variation in the recovery time in the group given 20 µg kg\(^{-1}\) and we therefore estimated the time by which 95% of patients would be expected to have reached an adequate level of recovery (ERT\(_{95}\)).

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean T1:T0 at antagonism (%)</th>
<th>Dose of neostigmine (µg kg(^{-1}))</th>
<th>ERT(_{95}) (min)</th>
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<tr>
<td>C</td>
<td>9</td>
<td>40</td>
<td>6.2</td>
</tr>
<tr>
<td>E</td>
<td>46</td>
<td>20</td>
<td>10.3</td>
</tr>
<tr>
<td>F</td>
<td>44</td>
<td>40</td>
<td>3.9</td>
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TABLE II. Times by which 95% of the population sampled would be expected to satisfy the criteria of antagonism (T1:T0 = 0.9 and T4:T1 = 0.7) calculated from the distribution of times to recovery of individual patients: estimated recovery time for 95% (ERT\(_{95}\))
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(table II). This approach is analogous to the concept of ED₉₅ in relation to drug doses. We suggest that the use of ERT₉₅ may be more relevant to patient management than consideration of mean recovery time in isolation.

There was no electromyographic or clinical evidence that the largest dose of neostigmine (40 µg kg⁻¹) produced slower recovery because of "neostigmine block", regardless of whether it was given as a single dose or as a supplement. This finding is not surprising: Payne and colleagues found that neostigmine 2.5 mg produced neuromuscular block only in those patients who had not received a neuromuscular blocking agent [21].

The pattern of train-of-four recovery in this study was similar to that found previously during spontaneous recovery from vecuronium [22]. This suggests that neostigmine does not exert a predominant influence on either pre- or post-junctional receptors [23].

We conclude that evoked recovery from vecuronium-induced block was most rapid after neostigmine 40 µg kg⁻¹ at both minimal and moderate degrees of spontaneous recovery. Recovery was prolonged when the dose was reduced, and the omission of neostigmine would clearly be unsatisfactory. The dose of neostigmine should not be reduced to less than 40 µg kg⁻¹, even when the single response had recovered to 50% of control and there are four responses to TOF stimulation.

ACKNOWLEDGEMENT

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REFERENCES