Optimum dose of neostigmine at two levels of atracurium-induced neuromuscular block


SUMMARY

There is controversy about the optimum dose of neostigmine for antagonizing neuromuscular block. We have studied 57 patients undergoing gynaecological surgery to establish a dose-response relationship when neostigmine was given to antagonize atracurium-induced block. Anaesthesia was induced with thiopentone and fentanyl and maintained with nitrous oxide and enflurane in oxygen and neuromuscular block was produced with a bolus of atracurium 0.5 mg kg\(^{-1}\). At the time of antagonism of block, three groups received neostigmine 20, 40 or 80 \(\mu\)g kg\(^{-1}\) at 5–10% recovery of the compound muscle action potential of the adductor pollicis (profound block) and three groups received one of these doses at 40–50% neuromuscular recovery (light block). At profound block, antagonism was prolonged by reducing the dose of neostigmine from 40 \(\mu\)g kg\(^{-1}\) to 20 \(\mu\)g kg\(^{-1}\), but not shortened by increasing the dose from 40 \(\mu\)g kg\(^{-1}\) to 80 \(\mu\)g kg\(^{-1}\). At light block, there was no significant difference between the three groups in the time taken to reach a train-of-four ratio of 0.7.

The optimum dose of neostigmine required to antagonize the extremes of surgical neuromuscular block produced by atracurium has yet to be defined satisfactorily.

The results of previous studies are conflicting on the relative advantages of neostigmine 2.5 mg (40 \(\mu\)g kg\(^{-1}\)) or 5.0 mg (80 \(\mu\)g kg\(^{-1}\)) for antagonism of profound block (> 90% twitch depression) [1,2]. One study has suggested that it may be possible to reduce the dose of neostigmine to less than 2.5 mg without jeopardizing the quality of antagonism of profound atracurium-induced block [3]. Anecdotal evidence suggests that several dose regimens are in common use, but no comparative study has been published.

There is little information on which to base the choice of dose of neostigmine when neuromuscular block produced by atracurium has waned towards the end of a surgical procedure and is of only moderate intensity (approximately 50% twitch depression). An excessive dose of neostigmine may enhance neuromuscular block produced by tubocurarine or gallamine when given at approximately 50% twitch depression [4], but it is not known if a single dose of neostigmine 5.0 mg constitutes an excessive dose for antagonism of atracurium-induced block.

At this moderate level of neuromuscular block (approximately 50% twitch depression), it would be interesting to know if the dose of neostigmine may be reduced safely to less than 2.5 mg; a strategy that might be expected to reduce the cardiovascular side effects of neostigmine. A previous investigation of the pattern of antagonism of vecuronium suggested that, even when substantial spontaneous recovery had occurred, reducing the dose of neostigmine to less than 40 \(\mu\)g kg\(^{-1}\) (2.5 mg) was associated with delayed antagonism [5].

In this study, we have investigated the following questions:

- During profound block (twitch depression greater than 90%), is a dose of neostigmine 40 \(\mu\)g kg\(^{-1}\) (approximately 2.5 mg) adequate or should this be increased to 80 \(\mu\)g kg\(^{-1}\) (approximately 5.0 mg)?
- When considerable spontaneous recovery from atracurium has occurred already (50% twitch depression), does increasing the dose of neostigmine from 40 \(\mu\)g kg\(^{-1}\) to 80 \(\mu\)g kg\(^{-1}\) increase the rate of antagonism or is antagonism complicated by neostigmine-induced block?
- At 50% twitch depression, is the quality of antagonism impaired if the dose of neostigmine is reduced from 40 \(\mu\)g kg\(^{-1}\) to 20 \(\mu\)g kg\(^{-1}\) (approximately 1.25 mg)?

**KEY WORDS**

Neuromuscular relaxants, atracurium, Antagonists, neuromuscular relaxants: neostigmine.

**PATIENTS AND METHODS**

The study was approved by the Hospital Ethics Committee and informed, written consent was obtained from all patients. We studied 57 patients...
undergoing elective gynaecological surgery; they were allocated randomly to one of six groups according to the dose of neostigmine to be given and the depth of neuromuscular block at which antagonism was attempted. Patients received neostigmine 20 μg kg⁻¹, 40 μg kg⁻¹ or 80 μg kg⁻¹ at 5-10% or 40-50% spontaneous recovery of the first response of the train-of-four. Patients of ASA grades III-IV, obese patients (greater than 85 kg) and those suffering from neuromuscular disease were excluded.

Measurement of neuromuscular function

The integrated evoked compound electromyogram (EMG) of the adductor pollicis was recorded using a Relaxograph (Datex) which delivered supramaximal trains-of-four stimuli of 0.2 ms duration at 2 Hz every 20 s to the ulnar nerve at the wrist using silver-silver chloride electrodes. The ratio of the first EMG response to the control (before neuromuscular block) (T1/T0) and the ratio of the fourth response to the first response in the same train-of-four (T4/T1—TOF ratio) were recorded.

This study used two criteria to assess recovery of neuromuscular function: the time between the administration of neostigmine and attainment of a train-of-four ratio (TOF) of 0.7 and the Recovery Index (the time taken for the first response of the train-of-four to recover from 25% of the control value to 75% of the control value). A TOF ratio of 0.7 is frequently taken to indicate adequate clinical recovery and coincides with restoration of adequate vital capacity [6]. We did not analyse recovery index in those patients who had not achieved 25% recovery before the administration of neostigmine.

Anaesthesia and antagonism of neuromuscular block

We premedicated patients with diazepam 10 mg and droperidol 5 mg administered orally 1 h before operation. Anaesthesia was induced with thiopental 3-5 mg kg⁻¹ and fentanyl 2-3 μg kg⁻¹ and maintained with 70% nitrous oxide in oxygen supplemented by 0.5-1% enflurane as clinically indicated.

Ventilation was controlled to maintain normocapnia. A consistent control EMG response was established before administration of atracurium 0.5 mg kg⁻¹ as a bolus. Additional doses of atracurium 0.05 mg kg⁻¹ were given as required to establish before administration of atracurium capnia. A consistent control EMG response was indicated.

Supplementation by 0.5-1% enflurane as clinically accepted as significant). This study used two criteria to assess recovery of neuromuscular function: the time between the administration of neostigmine and attainment of a train-of-four ratio (TOF) of 0.7 and the Recovery Index (the time taken for the first response of the train-of-four to recover from 25% of the control value to 75% of the control value). A TOF ratio of 0.7 is frequently taken to indicate adequate clinical recovery and coincides with restoration of adequate vital capacity [6]. We did not analyse recovery index in those patients who had not achieved 25% recovery before the administration of neostigmine.

TOF ratio was consistently greater than 0.7. Patients were observed in the recovery room for at least 2 h after operation.

Using a method published previously, a correction factor was obtained for each patient by taking into account the extent to which the first response of EMG train-of-four (T1) ultimately exceeded or failed to reach the initial control value [2]. This factor was expressed as a percentage which we used to adjust the recorded values of T1 to obtain corrected values.

Data analysis

We analysed data statistically using the Kruskal-Wallis test and pairwise comparisons were made using the Mann-Whitney U test with Bonferroni's correction for multiple comparisons (P < 0.05 was accepted as significant).

RESULTS

There were no significant differences between the six groups in mean age and weight (table I).

Profound block (5-10% recovery of T1: groups A, B and C): antagonism to a TOF ratio 0.7 took 8.3 min (median) after neostigmine 40 μg kg⁻¹ (table II). This time was not reduced significantly by increasing the dose of neostigmine to 80 μg kg⁻¹ (P = 0.19). Decreasing the dose to 20 μg kg⁻¹ significantly prolonged the time for antagonism, to 11.3 min (P = 0.04). Taking into account only the first response of the TOF, the Recovery Index was decreased by increasing the dose of neostigmine.

Table I. Patient details (mean (range)). Profound block: group A = neostigmine 20 μg kg⁻¹; group B = neostigmine 40 μg kg⁻¹; group C = neostigmine 80 μg kg⁻¹. Light block: group D = neostigmine 20 μg kg⁻¹; group E = neostigmine 40 μg kg⁻¹; group F = 80 μg kg⁻¹.

<table>
<thead>
<tr>
<th>Group A (n = 9)</th>
<th>Group B (n = 9)</th>
<th>Group C (n = 9)</th>
<th>Group D (n = 10)</th>
<th>Group E (n = 10)</th>
<th>Group F (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>34.8</td>
<td>37.4</td>
<td>38.7</td>
<td>38.4</td>
<td>33.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>60.1</td>
<td>63.6</td>
<td>64.0</td>
<td>59.5</td>
<td>64.6</td>
</tr>
<tr>
<td>(44-75)</td>
<td>(43-85)</td>
<td>(57-75)</td>
<td>(50-72)</td>
<td>(59-85)</td>
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profound neuromuscular block by using a dose of neostigmine less than
2.5 mg.
In both studies, in common with the current
investigation, antagonism of neuromuscular block was accepted as adequate when the TOF ratio had reached 0.7. In the current study, when neostigmine was given during profound block, increasing the dose from 40 \( \mu \)g kg\(^{-1} \) to 80 \( \mu \)g kg\(^{-1} \) did not significantly increase the rate of antagonism measured by TOF ratio. However, the Recovery Index (derived from the first response of the train-of-four) apparently demonstrated more rapid recovery of neuromuscular function after the larger dose of neostigmine. This observation was anticipated: return of the first twitch depression was 10% of the control value. Jones, Parker and Hunter [3] suggested that it might be possible to antagonize satisfactorily the profound neuromuscular block produced by atracurium by using a dose of neostigmine less than 2.5 mg.

Several factors influence the characteristics of an-
tagonism of neuromuscular blocking drug, including choice of anaesthetic technique, the neuromuscular blocking agent used, the degree of block at the time of antagonism and the type and dose of the anticholinesterase drug [2, 3, 7, 8].

Assessment of the train-of-four fade is of more
physiological and clinical relevance than assessment
of single twitch height and, although the data for
antagonism of the first response of the train-of-four are presented for completeness, the TOF ratio represents a more stringent test of adequate an-
tagonism of neuromuscular block [9].

We used enflurane to maintain anaesthesia; al-
though this agent potentiates neuromuscular block, all patients had similar end-tidal concentrations of enflurane during the period of antagonism and any effect on the antagonism of residual block would be expected to be similar in each group.

It is a common finding that the EMG does not
ultimately reach the control value obtained before
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four EMG responses proportionally, so that the
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invariably given after a considerable period of time
had elapsed after commencement of the EMG
measurements, and it is unlikely that significant drift occurred during the period of antagonism.

**Profound block (5–10% recovery of T1)**

Our study suggests that, using the TOF ratio as the clinically appropriate index, increasing the dose of neostigmine from 40 to 80 \( \mu \)g kg\(^{-1} \) confers no statistically significant benefit in respect of time for antagonism. This is in contrast with the study of Beemer and colleagues [2], who demonstrated that the larger dose of neostigmine produced more rapid antagonism of profound neuromuscular block [2]. Differences in method may explain this apparent discrepancy. Unfortunately, their anaesthetic tech-
nique was not standardized; the volatile agent was not specified and approximately 25% of their patients did not receive an inhalation agent. In addition, a broad definition of profound block was accepted (0–10% recovery) and 33% of their patients received suxamethonium before adminis-
tration of neostigmine.

### DISCUSSION

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### Table II. Time taken to reach a train-of-four (TOF) ratio of 0.7, and Recovery Index after neostigmine 20, 40 or 80 \( \mu \)g kg\(^{-1} \) given at profound block (5–10% spontaneous recovery) or light block (40–50% spontaneous recovery) (median, range) (groups as in table I). *P < 0.05 compared with group B (neostigmine 40 \( \mu \)g kg\(^{-1} \)).

<table>
<thead>
<tr>
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<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
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<tr>
<td>Time to TOF 0.7 (min)</td>
<td>11.3 (9.3–15.7)</td>
<td>8.3 (4.1–13.3)</td>
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<tr>
<td>Recovery index (min)</td>
<td>4.2* (3.1–7.5)</td>
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Profound block (5–10% recovery of T1)

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### Fox, Keens and Utting [1], using a different
method, demonstrated that a second dose of neo-
stitgmine (2.5 mg) given 2 min after an initial dose of
2.5 mg, did not significantly accelerate antagonism of
neuromuscular block produced by atracurium when the first twitch depression was 10% of the control value. Jones, Parker and Hunter [3] suggested that it might be possible to antagonize satisfactorily the profound neuromuscular block produced by atracurium by using a dose of neostigmine less than 2.5 mg.

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Optimum Dose of Neostigmine

Light block (40–50% recovery of T1)

When spontaneous recovery had been permitted to reach 40–50%, there was no significant benefit in increasing the dose of neostigmine to more than 20 μg kg⁻¹ (corresponding to a dose of neostigmine approximately 1.25 mg in an adult) in respect of time to antagonism to a TOF ratio 0.7 (table II). The dose at which the "ceiling affect" of neostigmine becomes apparent would therefore appear to be reduced when neuromuscular transmission has recovered to a greater degree. When the largest dose of neostigmine was used in the light block group, despite monitoring the EMG for at least 30 min after administration of neostigmine, we were unable to demonstrate "neostigmine block" which would have been revealed either as prolonged antagonism or as recurarization.

References