ANTAGONISM OF VECURONIUM AND ATRACURIUM: COMPARISON OF NEOSTIGMINE AND EDROPHONIUM ADMINISTERED AT 5% TWITCH HEIGHT RECOVERY

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It has been shown that edrophonium can rapidly and reliably antagonize neuromuscular blockade induced by vecuronium (Foldes et al., 1981; Baird, Bowman and Kerr, 1982) and atracurium (Baird and Kerr, 1983; Jones, Pearce and Williams, 1984). In all these studies, spontaneous recovery had occurred to the extent that there were four responses to train-of-four (TOF) stimulation, or the height of the single twitch (TH) was at least 20% of control before antagonism was attempted. Edrophonium has appeared less satisfactory when administered at lesser degrees of spontaneous recovery (Hughes, Astley and Payne, 1984; Engbaek et al., 1985; Lavery, Mirakhur and Gibson, 1985; Rupp et al., 1986).

In a recent study (Caldwell, Robertson and Baird, 1986) the reversal of profound unquantifiable neuromuscular blockade by neostigmine 0.07 mg kg\(^{-1}\) or edrophonium 0.8 mg kg\(^{-1}\), of neuromuscular blockade induced by vecuronium or atracurium, was compared. Reversal was attempted when the height of the single twitch (TH) had recovered spontaneously to 5% of the control value. The evoked responses, initially single twitch, then train-of-four (TOF) were observed until the TOF ratio was 70%. Induced recovery from TH 5% to 25% was shorter following edrophonium than following neostigmine with both vecuronium (P < 0.05) and atracurium (P < 0.05). The recovery indices and times until TH was 75% of control and until the TOF ratio was 70% were not different. The time from a TH of 75% to a TOF ratio of 70% was shorter following neostigmine than following edrophonium with both vecuronium (P < 0.01) and atracurium (P < 0.01). Edrophonium had a much more variable effect on vecuronium than on atracurium. These results show that although the onset of action of edrophonium was faster than that of neostigmine, this did not lead to a faster clinical recovery, and antagonism by edrophonium may be delayed in a number of patients if vecuronium is the neuromuscular blocker.

SUMMARY

In 39 healthy patients antagonism, by neostigmine 0.07 mg kg\(^{-1}\) or edrophonium 0.8 mg kg\(^{-1}\), of neuromuscular blockade induced by vecuronium or atracurium, was compared. Reversal was attempted when the height of the single twitch (TH) had recovered spontaneously to 5% of the control value. The evoked responses, initially single twitch, then train-of-four (TOF) were observed until the TOF ratio was 70%. Induced recovery from TH 5% to 25% was shorter following edrophonium than following neostigmine with both vecuronium (P < 0.05) and atracurium (P < 0.05). The recovery indices and times until TH was 75% of control and until the TOF ratio was 70% were not different. The time from a TH of 75% to a TOF ratio of 70% was shorter following neostigmine than following edrophonium with both vecuronium (P < 0.01) and atracurium (P < 0.01). Edrophonium had a much more variable effect on vecuronium than on atracurium. These results show that although the onset of action of edrophonium was faster than that of neostigmine, this did not lead to a faster clinical recovery, and antagonism by edrophonium may be delayed in a number of patients if vecuronium is the neuromuscular blocker.

PATIENTS AND METHODS

Thirty-nine patients gave informed consent to their inclusion in this ethically approved study. Premedication was with papaveretum 10–20 mg i.m. plus hyoscine 0.2–0.4 mg i.m. approximately 1 h before operation. Anaesthesia was induced using thiopentone 4–5 mg kg\(^{-1}\) i.v. and maintained with 67% nitrous oxide and 1% halothane (inspired) in oxygen. Supramaximal stimuli
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(0.1 Hz for 0.2 ms) were delivered via subcutaneous electrodes to the ulnar nerve at the wrist, and the resultant evoked response of the adductor pollicis muscle was transduced and recorded using the Myograph 2000 neuromuscular transmission monitor (Biometer, Denmark).

The first 20 patients received vecuronium 40–60 μg kg⁻¹ i.v. to achieve greater than 95% depression of TH. Tracheal intubation was performed once maximum depression of twitch height occurred, and IPPV instituted. When TH had recovered spontaneously to 5% of control, the patients were randomly selected to receive either neostigmine 0.07 mg kg⁻¹ plus atropine 1.2 mg i.v. or edrophonium 0.8 mg kg⁻¹ plus atropine 1.2 mg i.v. When TH exceeded 75% of control, the stimulation mode was changed to TOF and monitoring was continued until the TOF ratio reached 70%.

Measurements were made from the end of the injection of the antagonizing agent; T25 (time to TH of 25%); T75 (time to TH of 75%); recovery index (time from 25 to 75% TH) and Dur₇₀ (time to a TOF ratio of 70%).

Using the same design, a further 19 patients were studied, neuromuscular blockade being induced by atracurium 150–200 μg kg⁻¹ i.v.

Statistical analysis of the results was by the Mann–Whitney U test. P < 0.05 was considered significant.

RESULTS

There were no differences in the physical characteristics of the patients studied (table I).

The initial antagonism of both vecuronium and atracurium, as measured by the T25, was more rapid following edrophonium than following neostigmine. In contrast, the recovery index, T75 and Dur₇₀ were not different. The time interval from a TH of 75 to a TOF ratio of 70% (T75–Dur₇₀) was also analysed. This interval was significantly shorter in patients who received neostigmine compared with those who received edrophonium (tables II and III). The results are illustrated graphically in figure 1.

DISCUSSION

The present study confirms that edrophonium had a more rapid onset of action (T25) than neostigmine. There was no difference in the recovery index. Subsequent recovery (from TH 75% to TOF 70%) was more rapid following neostigmine than following edrophonium.
Fig. 1. Recovery times (mean ± SEM) for each combination of vecuronium (V), atracurium (A), neostigmine (N) and edrophonium (E). Times from end of injection of antagonizing agent (twitch height 5%) to twitch height 25% (T25) and 75% (T75) and to a train-of-four ratio of 70% (Dur70).

total times from injection of reversal agent to satisfactory clinical recovery (TOF 70%) were not statistically different. Edrophonium had a much more variable effect than neostigmine against vecuronium as suggested by the large standard deviations in Dur70 and T75–Dur70 in table II.

Engbaek and colleagues (1985) reported reversal of vecuronium at 10% TH recovery and found that the time to achieve a TOF of 70% was shorter following neostigmine 0.04 mg kg⁻¹ than following edrophonium 0.75 mg kg⁻¹. This difference was abolished by using a larger dose of edrophonium (1.5 mg kg⁻¹). The dose ratio of edrophonium to neostigmine, 40:1, used by these authors, was greater than the previously reported equipotent ratio of between 12:1 and 16:1 (Baird, Bowman and Kerr, 1982; Cronnelly, Morris and Miller, 1982; Bevan et al., 1984). A further difference in technique between that study and the present one is that Engbaek and his colleagues (1985) used a continuous i.v. infusion of neuromuscular blocking agent.

Many authors have studied the antagonism of neuromuscular blockade by edrophonium, and neostigmine. However, the results are difficult to compare because of the different anaesthetic, stimulating and recording techniques used. In addition, the level of TH recovery when the antagonist is injected and the selected end-point of satisfactory recovery, vary considerably from one study to the next. For example, although Rupp and co-workers (1986) also showed that, when antagonizing vecuronium-induced neuromuscular blockade at less than 10% TH recovery, increasing the dose of edrophonium from 0.5 mg kg⁻¹ to 1 mg kg⁻¹ abolished the delayed recovery of neuromuscular transmission when compared with neostigmine 0.04 mg kg⁻¹, their study only looked at recovery to a TH of 90%. The present study showed no difference in the total recovery times following edrophonium 0.8 mg kg⁻¹ or neostigmine 0.07 mg kg⁻¹, but when the constituent phases of recovery were examined in more detail (tables II and III), differences began to emerge which may be of importance in clinical practice.

A TH of 5% is close to the first clinically detectable recovery of neuromuscular transmission using TH or TOF stimulation modes. A TOF ratio of 70% is widely accepted as the desired end-point of clinical recovery. These are the starting and end-points in the present study. It has been demonstrated that patients with protected airways are usually able to ventilate adequately before TH has recovered to 75% of control (Hackett, Hughes and Payne, 1986). The present study shows that the times from a TH recovery of 75% to a TOF ratio of 70% are longer (up to 28 min) following edrophonium than following neostigmine (up to 8 min). If patients are discharged from theatre merely when spontaneous ventilation appears adequate, they may be “at risk” during this T75–Dur70 period.

If the selected recovery end-point falls within the initial rapid effect of edrophonium, then edrophonium will appear more effective than neostigmine. The more consistent and sustained effect of neostigmine against both vecuronium and atracurium has been previously demonstrated (Caldwell, Robertson and Baird, 1986). These results, along with those of the present study, suggest that neostigmine is the preferred antagonist.
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REFERENCES


