DOSE-RESPONSE RELATIONSHIPS FOR EDROPHONIUM AND NEOSTIGMINE ANTAGONISM OF MIVACURIUM-INDUCED NEUROMUSCULAR BLOCK

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SUMMARY

We have studied the dose-response relationships for neostigmine and edrophonium during antagonism of neuromuscular block induced by mivacurium chloride. Sixty-four ASA group I or II adults were given mivacurium 0.15 mg kg⁻¹ during fentanyl-thiopentone-nitrous oxide-isoflurane anaesthesia. Train-of-four stimulation (TOF) was applied to the ulnar nerve every 10 s, and the force of contraction of the adductor pollicis muscle was recorded. When spontaneous recovery of first twitch height reached 10% of its initial control value, edrophonium 0.1, 0.2, 0.4, or 1 mg kg⁻¹ or neostigmine 0.005, 0.01, 0.02, or 0.05 mg kg⁻¹ was administered by random allocation. Neuromuscular function in another 16 subjects was allowed to recover spontaneously. Spontaneous recovery from 90% mivacurium block to 95% twitch height and TOF ratio 0.75 occurred within 15 min. This study demonstrated that the dose-response curves for these two drugs for antagonism of neuromuscular block (first twitch and train-of-four ratio) were parallel. The doses of neostigmine required to achieve 50% (ED₅₀) and 70% (ED₇₀) recovery of the first twitch after 10 min were 2 (1.5-2.5) μg kg⁻¹ and 4.7 (4.1-5.4) μg kg⁻¹ (mean (95% confidence intervals)), respectively. Corresponding ED₅₀ and ED₇₀ values for edrophonium were 2.8 (0.75-10.2) μg kg⁻¹ and 9.2 (3.6-23.6) μg kg⁻¹, respectively. These values corresponded to neostigmine:edrophonium potency ratios of 1.4 (0.4-2.4) and 1.95 (0.9-2.9) for first twitch ED₅₀ and ED₇₀ height, respectively. The calculated doses producing 50% (ED₅₀) recovery of the TOF ratio at 10 min were neostigmine 2.57 (1.8-3.6) μg kg⁻¹ and edrophonium 26.9 (14.6-49.6) μg kg⁻¹. These values corresponded to a potency ratio of 10.4 (0.7-20). (Br. J. Anaesth. 1993; 71: 709-714)

KEY WORDS


Mivacurium chloride is a newly developed bisbenzylisoquinolinium non-depolarizing neuromuscular blocking agent. It has a short duration of action in experimental animals [1] and in humans [2, 3]. It is hydrolysed by butyrylcholinesterase (plasma cholinesterase) at a rate 70-88% of that of suxamethonium [1, 4]. As both this enzyme and acetylcholinesterase are inhibited by anticholinesterase drugs, Savarese and colleagues [1] have expressed some concern regarding the effect of cholinesterase inhibitors on the antagonism of mivacurium-induced neuromuscular block. Cook and colleagues [5] reported that the recovery index from mivacurium-induced block was shortened by administration of either neostigmine or edrophonium. They noted, however, that neostigmine in clinically relevant concentrations significantly inhibits the metabolism of mivacurium in vitro. In contrast, edrophonium and suxamethonium have no effect on the in vitro metabolism of mivacurium [5]. Although it has been suggested that the inhibition of the cholinesterases by edrophonium occurs by a mechanism different than that of neostigmine [6], observations reported by several investigators [5, 7] strongly support the contention that edrophonium does not inhibit butyrylcholinesterase. Therefore edrophonium may be the preferred antagonist of mivacurium block. Further, it has been suggested that anticholinesterase drugs may have effects other than inhibition of acetylcholinesterase at the neuromuscular junction [8, 9].

The dose-response relationships for edrophonium and neostigmine after mivacurium have not been studied. Therefore, this study was designed to establish dose-response relationships for edrophonium and neostigmine as antagonists of mivacurium-induced neuromuscular block.

PATIENTS AND METHODS

After obtaining institutional approval and informed consent, we studied 80 ASA group I or II patients of both sexes, aged 18-52 yr (mean 32.4 yr) and weights 45-90 kg (mean 68.2 (SD 11.3) kg). All patients were undergoing elective procedures, had no neuro-
muscular, renal or hepatic disease, and were not taking any drug known to interfere with neuromuscular function. All patients received oral lorazepam 2 mg 90 min before operation. An infusion of lactated Ringer's solution was given i.v. before induction of anaesthesia. ECG, pulse oximetry and arterial pressure were monitored. Temperature was monitored by a nasopharyngeal thermistor and maintained at 36.5 ± 0.5 °C. Anaesthesia was induced with fentanyl 2 μg kg⁻¹ and thiopentone 3-5 mg kg⁻¹, and was maintained with 70% nitrous oxide and 0.5–1% inspired isoflurane in oxygen. Concentrations of isoflurane, nitrous oxide, oxygen and carbon dioxide were measured continuously by a multiple-gas analyser (Capnomac, Datex Instrumentarium Corporation, Helsinki, Finland). Ventilation was adjusted to maintain normocapnia (end-tidal partial pressure of carbon dioxide (P E CO₂) 4.6–5.3 kPa).

The ulnar nerve was stimulated supramaximally at the wrist with square pulses of 0.2 ms duration, delivered in a train-of-four (TOF) sequence at 2 Hz every 10 s, using a Myotest peripheral nerve stimulator (Biometer International, Odense, Denmark). The resultant contraction of the adductor pollicis muscle was recorded using a force displacement transducer and neuromuscular function analyser (Myograph 2000, Biometer International, Odense, Denmark). Preload tension on the thumb was maintained at 300 g throughout the investigation. After a stable neuromuscular response was obtained, the patient received mivacurium 0.15 mg kg⁻¹ i.v. as a free-flowing bolus dose. Tracheal intubation was performed when neuromuscular response was abolished. Additional increments of mivacurium 0.1 mg kg⁻¹ were given to patients who required continued neuromuscular block, whenever the first twitch recovered to 10% of control value.

At the end of surgery, when first twitch height (T1) (the first response in the TOF) had recovered to 10% of control value, the patients received edrophonium 0.1, 0.2, 0.4 or 1 mg kg⁻¹, neostigmine 0.005, 0.01, 0.02 or 0.05 mg kg⁻¹ (n = 8 in each), or no antagonist drug (n = 16), by random allocation. Each dose of each antagonist agent was given to eight patients. Atropine, 0.3–1.5 mg, was administered when appropriate. No other antagonist was given for at least 10 min and the inspired isoflurane concentration was not altered. The TOF ratio (the amplitude of the fourth evoked response as a fraction of the first evoked response: T4/T1) was recorded continuously over the subsequent 10 min, at which point the dose–response study was concluded. Eight patients in the group who received no antagonist were allowed to recover spontaneously to a TOF ratio of 0.75. In all other patients, an additional dose of antagonist was given after 10 min if the TOF ratio was less than 0.75 or if the patient had clinical signs of inadequate neuromuscular function.

The results were subjected to probit transformation using PCNONLIN version 4.1 (ClinTrials, Inc., Lexington, Kentucky) [10]. Dose–response

**Fig. 1.** Mean first twitch height vs time after administration of various doses (mg kg⁻¹) of neostigmine (N) (---), edrophonium (E) (—) or in the spontaneous recovery group (SR) (—). Antagonism of neuromuscular block was attempted when first twitch height reached 10% of its control value. Confidence intervals have been omitted for the sake of clarity.

**Fig. 2.** Mean train-of-four ratio vs time after administration of various doses of neostigmine (N) (—), edrophonium (E) (—) or in the spontaneous recovery group (SR) (—). Antagonism of neuromuscular block was attempted when first twitch height reached 10% of its control value. Confidence intervals have been omitted for the sake of clarity.
relationships were calculated by linear regression of the probit transformation of T1 and TOF ratio on the logarithm of the dose. From these, the doses of antagonist expected to produce 50% and 70% recovery (ED50 and ED70) of T1 and TOF ratio were obtained every 1 min for 10 min after administration of the drug. Regression lines were compared using analysis of covariance. First, we tested the lines to determine if they deviated from parallelism; if they did not, an F test was applied to determine if the elevations were different. If so, a t test was applied to determine which line differed in elevation [11], using BMDP statistical package (University of California Press, 1990). Comparisons were made between the potencies of the antagonist drugs [12]. Recovery times of the first twitch from 25 to 75% and from 10 to 95% were compared using analysis of variance. Dunnett’s test was used to compare the spontaneous recovery group to each of the other groups. Results were expressed as means and 95% confidence intervals, and were considered statistically significant when P \leq 0.01.

RESULTS

Figures 1 and 2 show first twitch height and train-of-four ratio as a function of time after administration of the antagonist. At all doses, the effect of edrophonium was rapid and sustained; neostigmine had a slower onset. The largest doses of either edrophonium (1.0 mg kg$^{-1}$) or neostigmine (0.05 mg kg$^{-1}$) did not result in the greatest recovery of T1 or the TOF ratio, 10 min after antagonism (table I). The differences in recovery characteristics observed with edrophonium 1.0 mg kg$^{-1}$ compared with 0.4 mg kg$^{-1}$, or neostigmine 0.05 mg kg$^{-1}$ compared with 0.02 mg kg$^{-1}$ were not statistically significant (P > 0.05).

First twitch recovery 10 min after antagonism was greater (P < 0.01) in those patients who received edrophonium 0.1, 0.4 or 1.0 mg kg$^{-1}$ or neostigmine 0.05 mg kg$^{-1}$ than in those allowed to recover spontaneously (table I). Similar observations were noted for TOF recovery (table I). Similarly, time for the twitch height to recover from 25 to 75% and from 10 to 95% of the control value was significantly greater in the spontaneous recovery group compared with other groups (table I). In the absence of antagonist, the mean time required to attain a TOF ratio of 0.75 in the spontaneous recovery group was 15.4 (12.7–18.1) min. This was greater (P < 0.01) than times in other groups who received the antagonist agent (table I). It should be noted that not all patients who received anticholinesterase drugs recovered to a TOF ratio of 0.75 at 10 min, and none of the patients in the group who received neostigmine 0.005 mg kg$^{-1}$ had recovered to TOF of 0.75 by 10 min.

The dose-response relationships for T1 and TOF were calculated for each 1 min after administration of the antagonist (figs 3, 4). The slopes of the lines describing T1 and TOF recovery after edrophonium were not significantly different from the corresponding lines after neostigmine. The lines did not deviate from parallelism, but those constructed at 10 min were shifted significantly to the left compared with those constructed at 5 min (P < 0.001) for both antagonists. The calculated ED values for T1 height and TOF ratio from 4 min onward for edrophonium and neostigmine are presented in figures 5 and 6, respectively. Some of the calculated ED values are not reported because they were outside the range of doses tested.

The potency ratios, or the potency of neostigmine expressed as a multiple of that of edrophonium are presented in table II. For the train-of-four ED50 values, the potency ratio did not change with time. In contrast, the potency ratio for the first twitch decreased significantly at 10 min (table II).

DISCUSSION

This study demonstrated that the dose-response relationships of edrophonium and neostigmine antagonism of mivacurium neuromuscular block were parallel and that, in the absence of antagonist, spontaneous recovery (after return to 10% first twitch height) to a TOF ratio of 0.75 occurred in 15.4 (12.7–18.1) min.

The short duration of action of mivacurium is
related primarily to its hydrolysis by butyrylcholinesterase. A finding of particular interest was that both human butyrylcholinesterase and neostigmine were equally effective in antagonizing mivacurium in cats when antagonism was attempted at 90% block of twitch height [13]. However, in the presence of 100% twitch inhibition, Bownes and colleagues found that enzymatic antagonism through increased metabolism was more effective than antagonism by neostigmine [13]. Therefore, enzymatic antagonism would eliminate the concern regarding the antagonistic effect of neostigmine on metabolism of mivacurium [2]. Our results demonstrate that 25–75%, 10–95% recovery times of T1 and times to attain a TOF ratio of 0.75 were shorter (P < 0.01) following neostigmine- or edrophonium-induced recovery compared with spontaneous recovery (table I). Spontaneous recovery from 90% mivacurium block to 95% twitch height and TOF ratio of 0.75 occurred within 15 min (table I) and the average saving in time as a result of use of an antagonist was 7–9 min. Similar observations have been reported by others [2, 14]. Curran and colleagues [14] reported that, during nitrous oxide–oxygen–opioid anaesthesia, 25–75% recovery time of T1 was shorter after neostigmine 0.06 mg kg⁻¹ (mean 3 (SEM 0.2) min) compared with spontaneous recovery (6.5 (0.3) min).

Our data indicate that the potency ratio was not the same for single twitch and TOF. When reversal was attempted at 10% T1 recovery from mivacurium block, 5.4 times as much edrophonium as neostigmine was required to achieve 50% T1, but 11.39 times as much was needed to achieve a TOF ratio of 0.5 (table II). In this respect, our results are consistent with those of other investigators [15–17] who reported similar observations with other non-depolarizing neuromuscular blocking agents. It should be noted, however, that the increased dose requirements for both neostigmine and edrophonium to attain 70% recovery of T1 height was proportional, since the neostigmine:edrophonium potency ratios were similar (table II).

Donati and colleagues noted that, 10 min after injection of antagonist (after return to 10% first twitch height) the neostigmine:edrophonium potency ratio for T1 was approximately 20 for both atracurium and vecuronium [17], 12 for pancuronium and 16 for tubocurarine [15]. This is in contrast with a corresponding potency ratio of 1.4 observed in our study (table II). We noted that the potency ratio either decreased significantly after administration of the antagonist (as for T1) or did not change at all, as noted with the TOF response. This observation is at variance with other reports [15–17] and our own observations with rocuronium [18] and pipercuronium [unpublished data]. We interpret these observations jointly as suggesting
that neostigmine inhibition of mivacurium metabolism [5] was manifested by the increase in potency of edrophonium over time. This confirms that the neostigmine:edrophonium potency ratio varies depending on the agent used, depth of block and end-point chosen.

The introduction of mivacurium into anaesthetic practice allows provision of clinical relaxation for periods of 15 min to 3 h or more. When mivacurium is administered to provide paralysis for surgical procedures of short (15–20 min) duration, to wait an additional 9 min, on average, for adequate spontaneous recovery to occur would represent an approximately 50% prolongation of the surgical time. If mivacurium infusions were to be used for longer surgical procedures, then allowing spontaneous recovery to occur could be advantageous.

In summary, the results of this study demonstrate that spontaneous recovery from 90% mivacurium block to 95% twitch height and TOF ratio of 0.75 occurred within 15 min. It also emphasizes that both neostigmine and edrophonium are able to produce

| TABLE II. Potency in relation to doses required for 50% (ED_{50}) and 70% (ED_{70}) recovery of first twitch height and for 50% (ED_{50}) train-of-four recovery, 5 and 10 min after injection of antagonist (mean (95% confidence intervals)) |
|--------------------------------------------------|------------------|------------------|---------------------|
|                                                  | 5 min            | 10 min           | P                   |
| First twitch recovery                            |                  |                  |                     |
| ED_{50}                                          |                  |                  |                     |
| Edrophonium (μg kg\(^{-1}\))                     | 44.3 (35.8-54.8) | 2.8 (0.75-10.2)  | < 0.0001            |
| Neostigmine (μg kg\(^{-1}\))                     | 8.2 (7.3-9.2)    | 2.0 (1.5-2.5)    | 0.0001              |
| Potency ratio                                    | 5.4 (3.9-6.8)    | 1.4 (0.4-2.4)    | 0.01                |
| ED_{70}                                          |                  |                  |                     |
| Edrophonium (μg kg\(^{-1}\))                     | 103 (90.9-117)   | 9.2 (3.6-23.6)   | < 0.0001            |
| Neostigmine (μg kg\(^{-1}\))                     | 24.6 (21.9-27.6) | 4.7 (4.1-5.4)    | < 0.0001            |
| Potency ratio                                    | 4.18 (3.8-4.5)   | 1.99 (0.9-2.9)   | 0.0003              |
| Train-of-four recovery                           |                  |                  |                     |
| ED_{50}                                          |                  |                  |                     |
| Edrophonium (μg kg\(^{-1}\))                     | 302 (260-352)    | 26.9 (14.6-49.6) | < 0.0001            |
| Neostigmine (μg kg\(^{-1}\))                     | 26.5 (22.6-31)   | 2.57 (1.8-3.6)   | 0.0001              |
| Potency ratio                                    | 11.39 (10.5-12.3)| 10.4 (0.7-20)    | ns                  |
dose-dependent antagonism of mivacurium-induced block. The dose–response curves for edrophonium and neostigmine were parallel. The potency ratio is not the same for single twitch and train-of-four responses. Edrophonium was less capable of antagonizing fade (potency ratio of 11.39–10.4) than first twitch (potency ratio of 1.1–5.4).

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REFERENCES


