Dose-response relationships for edrophonium antagonism of mivacurium-induced neuromuscular block during N₂O-enflurane-alfentanil anaesthesia

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The purpose of this study was to determine the dose-response relationships for edrophonium antagonism of mivacurium-induced neuromuscular block. Seventy-five ASA I or II adults were given mivacurium $0.15 \text{ mg} \cdot \text{kg}^{-1}$ followed by an infusion ($7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) during alfentanil-propofol-N₂O-enflurane anaesthesia. Train-of-four stimulation (TOF) was applied to the ulnar nerve every 20 sec and the response of the adductor pollicis was recorded (Relaxograph NMT-100, Datex, Helsinki, Finland). Mivacurium infusion was modified at five-minute intervals in order to keep the height of the first twitch in TOF (T_1) at 5% of its control value. At the end of surgery, edrophonium (0.0, 0.125, 0.25, 0.5, or $1.0 \text{ mg} \cdot \text{kg}^{-1}$) combined with glycopyrrolate (0.0, 0.0012, 0.0025, 0.005, or $0.01 \text{ mg} \cdot \text{kg}^{-1}$) were administered by random allocation. Edrophonium doses of 0.25, 0.5 and $1.0 \text{ mg} \cdot \text{kg}^{-1}$ were different from placebo with regard to time to attain a TOF ratio (fourth twitch in TOF/ T_1) = 0.7 (13.8 ± 4.5 , 11.1 ± 3.5 , 11.4 ± 3.0 vs $19.7 \pm 4.7 \text{ min}$ $P < 0.05$). Doses of 0.5 and $1.0 \text{ mg} \cdot \text{kg}^{-1}$ permitted faster recovery time of T_1 from 10 to 95% (T_{10-95}) than did placebo (7.5 ± 3.8 , 8.9 ± 3.5 vs $14.5 \pm 5.0 \text{ min}$ $P < 0.05$). Edrophonium $0.5 \text{ mg} \cdot \text{kg}^{-1}$ was different from placebo with regard to recovery time of T_1 from 25 to 75% (T_{25-75}) (3.3 ± 2.0 vs $6.7 \pm 2.0 \text{ min}$ $P < 0.05$). Only edrophonium $0.5 \text{ mg} \cdot \text{kg}^{-1}$ provided faster recovery than placebo with regard to all three indices. It is con-

cluded that edrophonium $0.5 + \text{glycopyrrolate } 0.005 \text{ mg} \cdot \text{kg}^{-1}$ allow the fastest recovery from a mivacurium-induced block during enflurane-N₂O anaesthesia.

Ce travail vise à établir l'effet de différentes doses d'édrophonium sur l'antagonisme du bloc neuromusculaire induit par le mivacurium. Une dose de mivacurium ($0.15 \text{ mg} \cdot \text{kg}^{-1}$) suivie d'une perfusion ($7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) a été administrée à 75 adultes (ASA I, II) sous anesthésie (alfentanil-propofol-N₂O-enflurane). On procédait alors à une stimulation "train-de-quatre" (TOF) du nerf cubital aux 20 sec et à l'enregistrement de la réponse à l'éminence thénar (Relaxograph NMT-100, Datex, Helsinki, Finlande). La vitesse de perfusion était modifiée aux cinq minutes afin de maintenir l'amplitude de la première stimulation du TOF (T_1) à 5% de la valeur contrôlée. À la fin de l'intervention, on administrait de façon aléatoire édrophonium (0.0, 0.125, 0.25, 0.5 ou $1.0 \text{ mg} \cdot \text{kg}^{-1}$) + glycopyrrolate (0.0, 0.0012, 0.0025, 0.005 ou $0.01 \text{ mg} \cdot \text{kg}^{-1}$). Les doses d'édrophonium de 0.25, 0.5 et $1.0 \text{ mg} \cdot \text{kg}^{-1}$ ont permis un retour plus rapide du ratio TOF (quatrième stimulation du TOF/ T_1) = 0.7 comparé au placebo (13.8 ± 4.5 , 11.1 ± 3.5 , 11.4 ± 3.0 vs $19.7 \pm 4.7 \text{ min}$ $P < 0.05$). La récupération du T_1 de 10 à 95% (T_{10-95}) s'est effectuée plus rapidement avec édrophonium 0.5 et $1.0 \text{ mg} \cdot \text{kg}^{-1}$ qu'avec le placebo (7.5 ± 3.8 , 8.9 ± 3.5 , vs $14.5 \pm 5.0 \text{ min}$ $P < 0.05$). Une dose de $0.5 \text{ mg} \cdot \text{kg}^{-1}$ a aussi permis une récupération accélérée du T_1 de 25 à 75% (T_{25-75}) (3.3 ± 2.0 vs $6.7 \pm 2.0 \text{ min}$ $P < 0.05$). Seul édrophonium $0.5 \text{ mg} \cdot \text{kg}^{-1}$ a permis une récupération accélérée des trois indices étudiés. Édrophonium 0.5 + glycopyrrolate $0.005 \text{ mg} \cdot \text{kg}^{-1}$ s'avère la combinaison optimale pour renverser le bloc du mivacurium en présence d'enflurane-N₂O.

Key words

ANTAGONISTS, NEUROMUSCULAR RELAXANTS:

edrophonium, mivacurium;

ANAESTHETICS, VOLATILE: enflurane.

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Mivacurium is a relatively new, shorter-acting benzylisoquinolinium non-depolarizing neuromuscular blocking agent hydrolyzed by butyrylcholinesterase (plasma cho-

linesterase).^{1,2} Its administration either by infusion or by intermittent bolus doses is not associated with accumulation in humans.³ Because of these properties and mivacurium's unique spontaneous recovery profile, selecting both the most suitable anticholinesterase and dosage are a matter of debate.³⁻⁶ In fact, antagonism with reversal agents may not be required.⁵ Edrophonium doses as small as $0.125 \text{ mg} \cdot \text{kg}^{-1}$ accelerate recovery from mivacurium neuromuscular block in patients during propofol- N_2O anaesthesia.⁷ However, because of its ability to facilitate non-depolarizing neuromuscular block, enflurane anaesthesia may present a different situation.⁸

Therefore, we designed this randomized study to establish dose relationships and compare variation in heart rate for edrophonium as antagonist of mivacurium-induced neuromuscular block during enflurane- N_2O -alfentanil anaesthesia.

Methods

The study protocol was approved by the Institutional Review Board of Maisonneuve-Rosemont Hospital. Informed consent was obtained from 75 ASA group I or II non-pregnant patients, aged 18–65 yr scheduled to undergo short-lasting elective procedures (<120 min) under general anaesthesia with tracheal intubation. Exclusion criteria included a history of neuromuscular, renal or hepatic disease, previous allergic reactions to any of the study drugs and usage of drugs known to interfere with neuromuscular function or heart rate. Patients who suffered from asthma or morbid obesity (Body Mass Index > 35%)⁹ and patients using antiemetic drugs were also excluded.

Patients received either lorazepam 1–2 mg *po* 90 min before surgery or no premedication. Upon arrival in the operating room, the usual monitoring was instituted. Anaesthesia was induced with alfentanil ($30 \text{ } \mu\text{g} \cdot \text{kg}^{-1}$) and propofol ($2 \text{ mg} \cdot \text{kg}^{-1}$) *iv*. Supramaximal stimulation of the ulnar nerve at the lower forearm was determined automatically by searching for the stimulus current needed to activate all the stimulated muscles (0–70 mA) and then adding 20% to this maximal current (Relaxograph NMT-100, Datex, Helsinki, Finland). Stimulation with square pulses of 0.1 msec duration, delivered in a train-of-four (TOF) sequence at 2 Hz every 20 sec then began and the resultant contraction of the adductor pollicis was recorded (integrated EMG). After a stable neuromuscular response was obtained, the patients received mivacurium $0.15 \text{ mg} \cdot \text{kg}^{-1}$ *iv* and tracheal intubation was performed. Anaesthesia was maintained with enflurane (0.5–1.5% end-tidal concentration: Capnomac Ultima, Datex, Helsinki, Finland) in combination with 70% N_2O in oxygen and intermittent alfentanil $3\text{--}5 \text{ } \mu\text{g} \cdot \text{kg}^{-1}$ *iv* administration. The ventilator was adjusted to maintain nor-

mocapnia (PETCO_2 32–36 mmHg) and temperature was monitored with an oesophageal probe. A mivacurium infusion (anaesthesia pump 3400, Graseby, Watford, Herts, UK) was initiated ($7 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) after intubation and the rate adjusted at five-minute intervals ($\pm 2 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) in order to maintain the height of the first twitch in TOF (T_1) at 5% of its control value (T_c). At the end of surgery, mivacurium infusion was discontinued and patients were randomly assigned to receive, immediately, edrophonium 0.125 (Group B), 0.25 (Group C), 0.5 (Group D) or $1.0 \text{ mg} \cdot \text{kg}^{-1}$ (Group E) combined with glycopyrrrolate 0.0012, 0.0025, 0.005 or $0.01 \text{ mg} \cdot \text{kg}^{-1}$, or no antagonist drug (saline placebo) (Group A). Enflurane and N_2O administration were maintained for 20 min or until the TOF ratio (the amplitude of the fourth evoked response in TOF as a fraction of T_1 : T_4/T_1) reached 0.7. The lungs were then ventilated with 100% O_2 until extubation and the patients were transferred to the recovery room where they stayed for one hour. Neuromuscular data analyzed included the amplitude of the first twitch as a fraction of its control value at the reversal of neuromuscular block (T_1/T_c), recovery time of the first twitch height from 25 to 75% (T_{25-75}), from 10 to 95% (T_{10-95}) and time necessary for TOF to reach 0.7. Patients were also assessed for bradycardia (lowest heart rate) following administration of the antagonists. Data were collected by the investigators or a trained member of the nursing staff.

Data are expressed as mean $\pm$ SD for all variables. In addition, ranges are reported for the different recovery indices of neuromuscular function. Continuous variables were analyzed using analysis of variance with Scheffe contrast test if necessary, and χ^2 tests were used for descriptive (categorical) variables. In all cases, *P* values < 0.05 were considered statistically significant.

Results

There were no differences among the five groups with regard to age, weight and height of the participants (Table I). At the end of surgery, upon discontinuing mivacurium infusion and injecting reversal drugs, there were no differences either with regard to end-tidal concentration of enflurane, oesophageal temperature and alfentanil and mivacurium received (Table II) among the five groups. The T_1/T_c values were similar in all five groups at the reversal of neuromuscular block (Table III). The T_{25-75} value was reduced only in Group D compared with Group A (3.3 ± 2.0 vs 6.7 ± 2.0 min). The T_{10-95} value was less in Groups D and E than in Group A (7.5 ± 3.8 and 8.9 ± 3.5 vs 14.5 ± 5 min). The mean time required to attain a TOF ratio of 0.7 was less in Groups C, D and E than in Group A (13.8 ± 4.5 , 11.1 ± 3.5 and 11.4 ± 3.0 vs 19.7 ± 4.7 min) (Table III).

TABLE I Group characteristics

Group	A	B	C	D	E
Sex (M:F)	0:15	3:12	1:14	2:13	1:14
Age (yr)	35 ± 6	39 ± 10	37 ± 9	38 ± 9	32 ± 6
Weight (kg)	58 ± 11	65 ± 12	62 ± 8	62 ± 13	60 ± 13
Height (cm)	162 ± 6	165 ± 10	163 ± 5	164 ± 9	160 ± 4
Surgery*	13/1/1	9/2/4	9/3/3	11/2/2	11/2/2

Values are expressed as mean ± 1 SD ($n = 15/\text{group}$).

*Gynaecological laparoscopy/laparoscopic cholecystectomy/others.

TABLE II Characteristics at the end of surgery

Group	A	B	C	D	E
Mivacurium received (mg)*	15.2 ± 5.9	22.5 ± 12.8	24 ± 9.2	23.4 ± 17	20.5 ± 8.7
Alfentanil received (mg)*	1.9 ± 0.4	2.2 ± 0.6	2.5 ± 0.7	2.1 ± 0.8	2.0 ± 0.6
End-tidal enflurane (%)	1.0 ± 0.1	1.1 ± 0.3	1.1 ± 0.2	1.1 ± 0.3	1.0 ± 0.1
Duration of surgery (min)	48 ± 19	53 ± 25	67 ± 34	44 ± 19	46 ± 12
Oesophageal temperature (C°)	36.2 ± 0.7	35.9 ± 0.5	35.6 ± 0.6	36.0 ± 0.6	35.7 ± 0.6

Values are expressed as mean ± 1 SD ($n = 15/\text{group}$).

*During surgery.

TABLE III First twitch (T_1) and train-of-four (TOF) recovery

Group	A	B	C	D	E
T_1/T_c (%) at reversal	7 ± 3	8 ± 3	7 ± 3	7 ± 4	8 ± 3
T_{25-75} (min)	6.7 ± 2.0 [4.0–11.3]	5.6 ± 2.9 [1.3–11.8]	5.2 ± 3.4 [1.6–13.0]	3.3 ± 2.0* [0.6–8.3]	4.0 ± 1.6 [1.8–7.0]
T_{10-95} (min)	14.5 ± 5.0 [8.0–26.6]	11.6 ± 4.8 [3.0–19.6]	10.2 ± 3.1 [5.3–16.6]	7.5 ± 3.8† [2.3–16.2]	8.9 ± 3.5† [4.6–13.3]
Time to TOF ratio = 0.7 (min)	19.7 ± 4.7 [14.0–29.6]	15.2 ± 5.1 [8.6–25.3]	13.8 ± 4.5‡ [9.6–25.3]	11.1 ± 3.5‡ [5.6–19.0]	11.4 ± 3.0‡ [7.0–18.6]

Values are expressed as mean ± 1 SD and [range] ($n = 15/\text{group}$).

* $P < 0.05$ vs group A.

† $P < 0.05$ vs group A.

‡ $P < 0.05$ vs group A.

Mean heart rate decreased in all five groups following administration of the antagonists. This also occurred in the placebo group since surgical stimulation ceased at the same time. Slowing of the heart rate was greater in Group C than in Group A (68 ± 13 to 55 ± 5 vs 71 ± 10 to 65 ± 4 beats $\cdot$ min $^{-1}$) (Table IV). Two patients, one in Group B, the other in Group E, received atropine 0.2 mg *iv* when their heart rates decreased respectively from 42 to 34 and 45 to 37 beats $\cdot$ min $^{-1}$ following administration of the antagonists.

Discussion

We intended to study spontaneous recovery from an intense mivacurium-induced neuromuscular block in patients under enflurane-N₂O anaesthesia and establish if various doses of edrophonium could accelerate that recovery. Our data showed that edrophonium 0.125

mg $\cdot$ kg $^{-1}$ does not reduce the usual indices (T_{25-75} , T_{10-95} , time to TOF ratio = 0.7) of neuromuscular recovery. In dosages ranging from 0.25 to 1.0 mg $\cdot$ kg $^{-1}$, edrophonium presents an advantage over placebo with regard to at least one studied index. However, only in a dose of 0.5 mg $\cdot$ kg $^{-1}$ was edrophonium superior to spontaneous recovery for all three indices. Recovery is then 30 to 45% faster, resulting in an approximate gain of nine minutes to reach a TOF ratio = 0.7 (Table III). We did not find any clinically relevant difference with regard to incidence of bradycardia. The only significant difference was a modest decrease in heart rate in patients receiving edrophonium 0.25 mg $\cdot$ kg $^{-1}$ $\pm$ glycopyrrolate 0.0025 mg $\cdot$ kg $^{-1}$ compared with those in the placebo group (Table IV).

Bryson *et al.* reported that, during N₂O-propofol-opioid anaesthesia, recovery time to TOF = 0.7 from

TABLE IV Decrease in heart rate following administration of reversal drugs

Group	A	B	C	D	E
Heart rate at reversal (beats · min ⁻¹)	71 ± 10	63 ± 11	68 ± 13*	69 ± 9	63 ± 9
Lowest heart rate following reversal (beats · min ⁻¹)	65 ± 4	54 ± 4	55 ± 5*	59 ± 7	58 ± 5

Values are expressed as mean ± 1 SD ($n = 15$ /group).

* $P < 0.05$ vs Group A.

a mivacurium block was shorter after edrophonium 0.125 mg · kg⁻¹ than with spontaneous recovery ($P = 0.01$).⁷ This is at variance with our results but, unlike our study, they attempted to maintain T_1 at 10% of its control value. It is also possible that enflurane was responsible for the ineffectiveness of such small doses in our study. Enflurane^{3,8,10} and isoflurane¹¹ have both been shown to reduce mivacurium requirements. Enflurane, administered to maintain end-expired concentration between 0.9 and 1.2% can effectively decrease mivacurium ED₅₀ by 30%¹⁰ but its influence on recovery profile may be less significant. Shanks,³ who studied spontaneous recovery following mivacurium administration either with a bolus dose or an infusion observed that enflurane (end-expired concentration = 1.26%) did not affect the recovery profile when compared with an opioid-barbiturate-N₂O technique but their patients received no reversal drugs. Poler¹² also reported that the recovery period following mivacurium administration was similar whether enflurane (end-expiratory concentration 0.75%) was or was not part of the anaesthesia technique but, unlike us, they used neostigmine and attempted reversal of less intense block (T_1 depression at reversal = 55%). Naguib *et al.* studied the recovery profile from mivacurium-induced block following variable doses of edrophonium during N₂O-fentanyl-isoflurane (end-expired concentration = 0.5–1.0%) anaesthesia.⁴ They found that the time required to attain a TOF ratio of 0.75 was eight to nine minutes shorter in patients who received edrophonium 0.4 mg · kg⁻¹ than in the spontaneous recovery group. This is in agreement with our data although they used isoflurane and attempted reversal when T_1 height was at 10% of its control value. On the other hand, these differences may explain why, contrary to us, they found that recovery of T_{25-75} , T_{10-95} and time to TOF = 0.75 were shorter in patients receiving edrophonium 0.1 mg · kg⁻¹ than in the spontaneous recovery group ($P < 0.01$).

The time to reach a TOF ratio = 0.7 is generally agreed upon as being one of the most clinically relevant measures of recovery.¹³⁻¹⁶ It is then important to note the wide range of results observed in our study whether or not reversal was attempted. We feel clinicians should be aware of such variability. Although the mean reduction in time to TOF ratio = 0.7 provided by edrophonium 0.5

mg · kg⁻¹ is a modest 8.6 min compared with placebo, its administration may be justified to avoid long spontaneous recovery periods lasting up to 29.6 min in our study.

In summary, our data show that edrophonium 0.125 mg · kg⁻¹ does not reduce the recovery time from mivacurium infusion-induced block compared with spontaneous recovery during N₂O-enflurane-alfentanil anaesthesia. Also, although doses of edrophonium 0.25 and 1.0 mg · kg⁻¹ can both shorten some of the recovery indices studied, edrophonium 0.5 mg · kg⁻¹ + glycopyrrolate 0.005 mg · kg⁻¹ is the only mixture associated with reductions in all three indices (T_{25-75} , T_{10-95} , time to TOF ratio = 0.7).

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