The reversal of profound mivacurium-induced neuromuscular blockade

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Purpose: *Mivacurium is metabolized by plasma cholinesterase catalyzed ester hydrolysis. Acetylcholinesterase antagonists used in the reversal of muscle relaxation may also inhibit plasma cholinesterase and, therefore, delay the hydrolysis of mivacurium. The clinical interaction between acetylcholinesterase antagonists and mivacurium induced neuromuscular blockade was studied.*

Method: *Intraoperative muscle relaxation was maintained with a mivacurium infusion to achieve a constant intense block (first twitch, T_1, 2–3% of control). Patients were randomly divided into three groups. Patients in Group 1 received no anticholinesterase, in Group 2 neostigmine 0.07 $mg \cdot kg^{-1}$, and in Group 3 edrophonium 1 $mg \cdot kg^{-1}$. The times between termination of the mivacurium infusion (Group 1) or the administration of the anticholinesterase (Groups 2 and 3) to 25%, 50%, 75% and 95% T_1 recovery , and to 50%, 70% and 90% recovery in the ratio, T_4/T_1 (TR) were recorded.*

Result: *In the neostigmine Group, T_1 recovery to 25%, 50% and 75% (2.32 ± 1.41, 3.90 ± 1.85 and 6.88 ± 2.66 min) was accelerated compared with control (3.36 ± 1.34, 5.78 ± 2.22, and 8.58 ± 3.60, and), but recovery to 95% (18.53 ± 9.09 vs 13.29 ± 5.24 min) was delayed. Also, TR recovery to 50%, 70%, and 90% was slower (14.47 ± 8.73, 21.25 ± 11.06 and 31.37 ± 12.11 min vs 11.75 ± 3.74, 13.78 ± 4.39 and 17.86 ± 6.44 min). However, all T_1 and TR recovery times were decreased in the edrophonium group (0.88 ± 0.51, 2.00 ± 1.50, 4.97 ± 2.96, and 9.35 ± 5.24 min for T_1 and 6.86 ± 3.93, 9.05 ± 4.51 and 12.24 ± 6.66 min for TR).*

Conclusion: *Neostigmine reversal of intense mivacurium neuromuscular block should be avoided, as this may result in prolongation of the block.*

Objectif: *Le mivacurium est hydrolysé par un ester catalysé pr la cholinestérase plasmatique. Les antagonistes de l'acetylcholinestérase utilisés pour inverser la relaxation musculaire peuvent aussi inhiber la cholinestérase plasmatique et, par conséquent, retarder l'hydrolyse du mivacurium. Cette étude portait sur l'interaction clinique entre les antagonistes de l'acétylcholinestérase et le bloc neuromusculaire induit par le mivacurium.*

Méthodes: *La relaxation musculaire peropératoire était maintenue par une perfusion de mivacurium pour procurer une curarisation profonde et continue (premier twitch, T_1, à 2–3% du contrôle). Les patients étaient répartis aléatoirement entre trois groupes. Les patients du groupe 1 ne recevaient pas d'anticholinestérase, le groupe 2, de la néostigmine 0,07 $mg \cdot kg^{-1}$ et le groupe 3, de l'édrophonium 1 $mg \cdot kg^{-1}$. Les intervalles entre l'arrêt de la perfusion de mivacurium (groupe 1) ou entre l'administration de l'anticholinestérase (groupes 2 et 3) et la récupération à 25%, 50%, 75% et 95% de T_1, et la récupération à 50%, 70% et 90% du rapport T_4/T_1 (TR) étaient enregistrés.*

Résultats: *Dans le groupe néostigmine, la récupération de T_1 à 25%, 50% et 75% (2,32 ± 1,41, 3,90 ± 1,85 et 6,88 ± 2,66 min) était accélérée comparativement au contrôle (3,36 ± 1,34, 5,78 ± 2,22 et 8,58 ± 3,60) mais la récupération à 95% (18,53 ± 9,09 vs 13,29 ± 5,24 min) était retardée. De plus, la récupération de TR à 50%, 70% et 95% se faisait plus lentement (14,47 ± 8,73, 21,25 ± 11,05 et 31,27 ± 12,11 min vs 11,75 ± 3,74, 13,78 ± 4,39 et 17,86 ± 6,4 min). Cependant, tous les intervalles de récupération à T_1 et de TR étaient diminués dans les groupes édrophonium (0,88 ± 0,52, 2,00 ± 1,50, 4,97 ± 2,96 et 9,35 ± 5,25 min pour T_1 et 6,86 ± 3,93, 9,05 ± 4,51 et 12,24 ± 6,66 min pour TR).*

Conclusion: *L'inversion par le néostigmine du bloc neuro-*

Key words

NEUROMUSCULAR RELAXANTS: mivacurium;
ANTICHOLINESTERASE: edrophonium. neostigmine;
ENZYMES: plasma cholinesterase.

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musculaire profond au mivacurium devrait être évitée, parce qu'il est possible qu'elle prolonge le bloc.

Mivacurium is a benzylisoquinoline muscle relaxant. Clinically, it is a short-acting, rapid-onset nondepolarizing neuromuscular blocker. The short duration can be explained by its rapid biotransformation (via plasma cholinesterase catalyzed hydrolysis of the ester bonds).[1,2] When a patient is given the recommended mivacurium intubation dose of 0.15 $mg \cdot kg^{-1}$, the clinical duration of muscle relaxation is approximately 15 min. The necessity for reversal of mivacurium-induced neuromuscular blockade in clinical anaesthesia is unsettled. While spontaneous recovery after mivacurium has been found to be satisfactory for many clinicians, the use of anticholinesterases to reverse mivacurium-induced muscle relaxation is effective.[3,4]

Recently, the duration of mivacurium-induced muscle relaxation was shown to be prolonged in patients with atypical plasma cholinesterase.[5–7] The molecular structures of plasma cholinesterase and of acetylcholinesterase are very similar.[8] Therefore, a non-competitive inhibitor of acetylcholinesterase may also inhibit plasma cholinesterase. Indeed, most of the clinically used anticholinesterases are also inhibitors of plasma cholinesterase.[9] In patients paralyzed with mivacurium in whom the relaxant was reversed with anticholinesterase, plasma cholinesterase activity would be decreased and the rate of mivacurium hydrolysis decreased. We studied electromyographic character of mivacurium induced profound neuromuscular blockade and anticholinesterase-induced reversal in surgical patients.

Methods

This study protocol was approved by the University of California Irvine Human Subjects Review Committee and informed consent was obtained from every subject. The 30 adult patients studied were ASA 1–2 and aged between 18 and 60 yr. Patients were scheduled for orthopaedic, gynaecological and plastic surgery under general anaesthesia. Patients with neurological, musculoskeletal, cardiovascular, or endocrinological pathology were excluded from the study. Anaesthesia was induced, after adequate denitrogenation, with 50 μg sufentanil, 2–4 $mg \cdot kg^{-1}$ thiopentone and 1–2 mg midazolam, *iv*. Tracheal intubation was facilitated with 0.15 $mg \cdot kg^{-1}$ mivacurium given over 30 sec. Anaesthesia was maintained with nitrous oxide, 70% in oxygen, plus incremental doses of sufentanil, 1 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ Isoflurane, up to 1%, was used when additional anaesthesia was required at the discretion of the anaesthetists.

Throughout the operative period, neuromuscular activity of the thenar muscle was monitored electromyographically with a Datex 221 neuromuscular transmission monitor (Datex 221 NMT) as previously described.[10] After the skin was degreased with an alcohol pad, five disposable electrodes were applied. Two stimulating electrodes were applied over the course of the ulnar nerve at the forearm. One ground electrode was applied at the palmar aspect of the wrist. Two sensing electrodes were applied over the thenar eminence. The calibration of the NMT for each patient was carried out after the induction of the anaesthesia but prior to the administration of mivacurium. These arrangements eliminated the potential interference caused by voluntary muscular activity in the awake patient and also reduced patient discomfort. After calibration, the NMT delivered a train of four (TOF) supramaximal stimulating currents at 2 Hz to the ulnar nerve. The resultant muscular depolarization electric signal intensity T_0 was established and served as reference for all subsequent EMG responses. The TOF stimuli were delivered continuously every 20 sec and the resultant EMG was used to assess the level of the neuromuscular blockade. The result was both digitally reported on a window and graphically plotted on a strip chart recorder.

The level of intraoperative muscle relaxation was maintained with a mivacurium infusion. The rate of the infusion was titrated to maintain the first twitch of the TOF at 2–3% of the pre-muscle relaxant reference intensity ($T_1/T_0 = 0.02 \sim 0.03$). When muscle relaxation was no longer required, the subjects were randomly assigned to one of three groups. Patients in Group 1 received no reversal agent. Patients in Group 2 received 0.07 $mg \cdot kg^{-1}$ neostigmine with 0.02 $mg \cdot kg^{-1}$ atropine *iv* and patients in Group 3 received 1 $mg \cdot kg^{-1}$ edrophonium with of 0.007 $mg \cdot kg^{-1}$ atropine *iv*. Neuromuscular activity was continuously monitored during the reversal process until the return of a normal response, with T_4/T_1 larger than 95%.

From the strip chart recorder, the graphic data presented two electromyographic values, T_1 and TR. The T_1 is the ratio of the first twitch response (T_1) of a TOF stimulation to the individually standardized twitch (T_0) (before the administration of any muscle relaxant) and TR is the ratio between the fourth twitch response intensity (T_4) to the first twitch response intensity (T_1) in a TOF stimulation ($TR = T_4/T_1$).

The times from the end of the mivacurium infusion in Group 1 or the administration of the reversal agents in groups 2 and 3, to 25%, 50%, 75%, and 95% recovery of T_1 were measured. Similarly, the times between the end of the mivacurium infusion in Group I or the administration of the reversal agents in Groups 2 and 3, and 50%, 70%, and 90% recovery of TR were measured.

TABLE I Patient profile

Treatment group	*Age – yr*	*Weight – kg*	*Mivacurium infusion rate* $\mu g \cdot kg^{-1} \cdot min^{-1}$
Spontaneous	28.6 ± 13.7	69.02 ± 7.9	6.8 ± 1.5
Neostigmine	32.5 ± 8.4	63.4 ± 14.32	6.9 ± 2.3
Edrophonium	31.9 ± 14.8	74.56 ± 12.77	7.2 ± 2.0

Mean ± SD.

TABLE II Recovery characteristics after profound mivacurium blockade

Treatment group	*Recovery to point*	*Mean time – min*	*SD – min*
Spontaneous	25% T_1	3.36	1.34
	50% T_1	5.78	2.22
	75% T_1	8.58	3.60
	95% T_1	13.29	5.24
	25–75% T_1	5.22	2.54
	50–95% T_1	7.51	3.41
Neostigmine	25% T_1	2.32	1.41
	50% T_1	3.90	1.85
	75% T_1	6.88	2.66
	95% T_1	18.53	9.09
	25–75% T_1	4.56	1.58
	50–95% T_1	14.64	8.45
Edrophonium	25% T_1	0.88*	0.51
	50% T_1	2.00*	1.50
	75% T_1	4.97*	2.96
	95% T_1	9.35†	5.24
	25–75% T_1	4.91	2.00
	50–95% T_1	7.35†	3.66

T_1 First twitch of train-of-four stimulation.
*$P < 0.05$ vs spontaneous recovery.
†$P < 0.05$ vs neostigmine.

We chose these parameters to characterize clinical recovery because 70% and 90% recoveries in TR have been used extensively to assess respiratory activities during recovery of the neuromuscular blockade.[11,12] The results among groups were compared and analyzed using analysis of variance (ANOVA), and the Bonferroni-Dunn test to correct for multiple comparisons. A $P < 0.05$ was considered statistically significant.

Results

The age, body weight and infusion rate of mivacurium required for muscle relaxation were similar among the three groups (Table I). T_1 recovery and TOF ratios for all three groups are listed in Tables II and III, respectively.

When patients were deeply paralyzed with mivacurium, the reversal characteristics of neostigmine and edrophonium were different. Compared with control, edrophonium and neostigmine both accelerated initial reversal (T_1 to 25%, 50%, and 75%) of mivacurium-induced neuromuscular blockade. Edrophonium also accelerate the late recovery (95%) while neostigmine delayed the late recovery. This difference can be better demonstrated by studied the TR. We found that its recovery was accelerated by edrophonium but prolonged by neostigmine at all levels studied (50%, 70% and 90%) (Figures 1 and 2).

TABLE III Train-of-four recovery characteristics of profound mivacurium blockade

Treatment group	*Recovery to:*	*Mean – min*	*SD – min*
Spontaneous	50%	11.75	3.74
	70%	13.78	4.39
	90%	17.86	6.44
Neostigmine	50%	14.47	8.73
	70%	21.25	11.06
	90%	31.37*	12.11
Edrophonium	50%	6.86†	3.93
	70%	9.05†	4.51
	90%	12.24	6.66

*$P < 0.05$ vs Group 1 and Group 2.
†$P < 0.05$ vs Group 2.

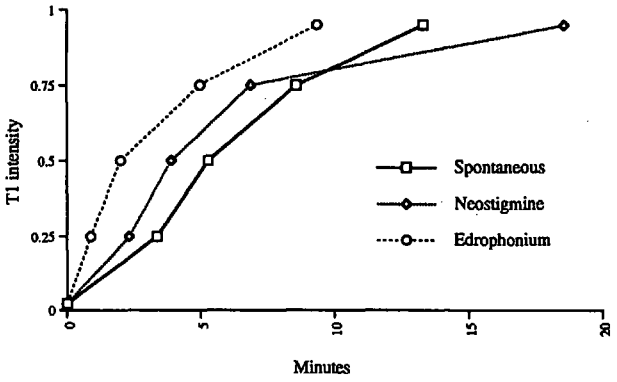

FIGURE 1 Recovery of neuromuscular blockade after mivacurium infusion (Group 1, spontaneous recovery) and the administration of neostigmine (Group 2) or edrophonium (Group 3).

Discussion

With profound neuromuscular blockade induced in these surgical patients by using mivacurium, reversal of the blockade with anticholinesterases (edrophonium and neostigmine) followed different courses. Compared with spontaneous recovery, edrophonium consistently accelerated the process whilst with neostigmine, the early

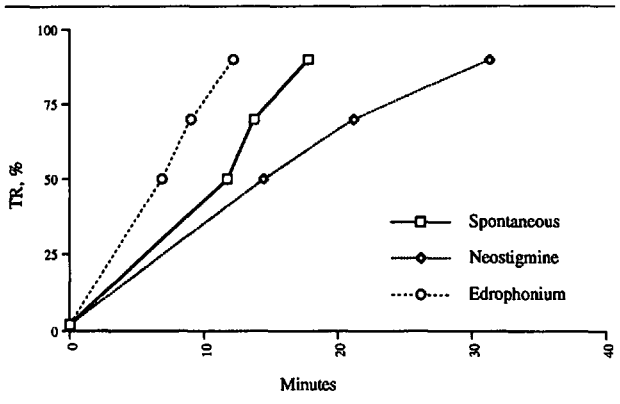

FIGURE 2 Recovery of neuromuscular blockade after mivacurium infusion (Group 1) and the administration of neostigmine (Group 2) or edrophonium (Group 3).

recovery was accelerated but total return of the neuromuscular function was delayed. The explanation for this phenomenon lies with the underlining biochemical mechanism of neuromuscular transmission.

The molecular mechanism of reversal of nondepolarizing neuromuscular relaxants involves inhibition of acetylcholinesterase. This inhibition can be either competitive (active site occupation) or noncompetitive (enzyme inactivation). Edrophonium, through its ionic interaction with the substrate binding site, inhibits the acetylcholinesterase by a competitive mechanism. The degree of inhibition depends upon the relative abundance of the inhibitor (edrophonium) and the substrate (acetylcholine) at the active site. The duration of edrophonium induced inhibition of acetylcholinesterase depends on the pharmacokinetic half-life of the inhibitor at the motor endplate area. Neostigmine inhibits acetylcholinesterase through inactivation of this enzyme by a modification of the active site (carbamylation). Once the derivatization is completed, the chemically altered enzyme molecule becomes inactivated. The inactivation lasts until spontaneous hydrolysis of the carbamylated enzyme regenerates the native enzyme. The chemical kinetic properties and the thermodynamic properties of the reactions dictate the partition of the enzyme molecules between the two different chemical identities, the active enzyme and the carbamylated enzyme. The pharmacokinetic half-life of noncompetitive reversal agents thus bears no direct relationship with the duration of their biological activity.

The molecular interactions between cholinesterase and these two classes of anticholinesterase agents are different. Edrophonium, in clinically achieved plasma concentrations, does not inhibit plasma cholinesterase.[16,15] Neostigmine, on the other hand, is a potent plasma cholinesterase inhibitor.[6,16–19] The effect of neostigmine, a noncompetitive anticholinesterase, on mivacurium induced neuromuscular blockade is the sum of two opposing factors one which favours blockade and one which opposes it.

Examination of compiled recovery characteristics from the individual electromyograms (Figures 1 and 2), revealed distinct recovery profiles. In the spontaneous recovery group, T_1 in the electromyograph is represented by a smooth sigmoid curve. The time between the two points of initial recovery and 50% recovery closely match the duration from point of 50% recovery to 95% recovery (5.78 ± 2.22 min versus 7.51 ± 3.41 min).

Reversal of mivacurium induced muscle relaxation by edrophonium is characterized by rapid return of T_1 twitch intensity to 50% of reference value (2.00 ± 1.50 min). Subsequent recovery from 50% to 95% was not accelerated, compared with spontaneous recovery (7.35 ± 3.66 min vs 7.51 ± 3.41 min). This observation suggests that:

1 Edrophonium has a limited role on the activity of the plasma cholinesterase and:
2 The short plasma half-life of mivacurium plays a dominant role during the time from 50% to 95% T_1 recovery.

The reversal of mivacurium induced deep neuromuscular blockade by neostigmine produced two distinct effects:

1 Initially, a reduced neuromuscular blockade level, as expected in patients receiving any nondepolarizing neuromuscular blocker, (T_1 returns to 50% in 3.90 ± 1.85 min compared with spontaneous recovery 5.78 ± 2.22 min) and
2 This is followed by a reduced rate of recovery. The slow recovery is especially prominent in the later phase of the recovery curve. Between 50% and 95% recovery of the first twitch in the train-of-four stimulation, the neostigmine group falls behind the spontaneous recovery group (14.64 ± 8.45 min vs 7.51 ± 3.41 min).

The ability to sustain muscle contraction is a better index, than single twitch response, of the state of recovery from neuromuscular blockade. *Fade*, or the ratio (TR) between fourth twitch, T_4 and the first twitch T_1, is probably the most meaningful clinical characteristic and most widely used reference in evaluating recovery of neuromuscular blockade.[13] Indeed, respiratory function measurements return to within 5% of pre-relaxant values, a point considered to represent adequate recovery, when neuromuscular function returns to 70% TR.[11] Subsequently, it was shown that TR must return to 90% before all clinical tests return to normal.[12] In the spontaneous recovery group, the TR recovered to 70% at 13.78

± 4.39 min and to 90% at 17.86 ± 6.44 min. When edrophonium was used to reverse the mivacurium induced blockade, it took 9.05 ± 4.51 min and 12.24 ± 6.66 min for TR to return to 70% and 90%, respectively. The reduction in time was either 4.7 or 5.6 min, depending on the end point selected. When neostigmine was used to reverse the blockade, it took 21.25 ± 11.06 min to return to TR 70% and 31.37 ± 12.11 min for return to 90% TR. The recovery of the neuromuscular blockade was delayed by the use of neostigmine: recovery of neuromuscular blockade to TR 70% and TR 90% was prolonged 7.5 and 13.5 min. A mathematical analysis of this situation is presented in the appendix.

Since isoflurane attenuates neuromuscular activity, it might be argued that our results were complicated by the introduction of this potent inhalational anaesthetic. We believe that, due to the random nature of group assignment, isoflurane may have altered the result quantitatively but not qualitatively.

Recently, Abdulatif showed that neostigmine was not as effective as edrophonium in reversing the profound neuromuscular blockade caused by mivacurium. However, there were no comparisons with spontaneous recovery.[20] Hart *et al.* showed that edrophonium was not as effective as a reversal agent for mivacurium as for vecuronium or *d*-tubocurarine induced muscle relaxation, and therefore advised against its use.[21] In a similar study, Szenohradszky *et al.* showed that neostigmine was less effective in reversing mivacurium induced muscle relaxation.[22] While these study designs may not correlate with the clinical situation, nevertheless, the notion that neostigmine is a better agent for mivacurium reversal was not supported.

In conclusion, we have observed a paradoxical phenomenon in the reversal of profound mivacurium-induced neuromuscular blockade. In patients with intense paralysis, reversal may or may not be benefited depending on the selection of reversal agent. While both edrophonium and neostigmine partially reverse blockade initially, neostigmine slows complete recovery compared with spontaneous recovery. Therefore, if reversal of intense block is desired, edrophonium, but not neostigmine, should be used.

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Appendix

After supramaximal electrical stimulation to the motor nerve, the resultant neuromuscular activity (NMA) is a function of the acetylcholine concentration (ACh) at the neuromuscular junction.

$$NMA = \Omega[ACh],$$

where Ω is the conversion factor.

Assuming that mivacurium neuromuscular blockade is caused by competitive inhibition of ACh-receptor interaction at the post-synaptic motor end plate:

$$NMA = k\Omega[ACh]/[Miva](t),$$

where NMA is the neuromuscular activity induced by electrical stimulation of the motor nerve, k is the efficiency ratio between acetylcholine and mivacurium molecules' competitive interaction with the acetylcholine receptor, [Miva](t) represents the concentration of mivacurium at the active site and is a function of time.

Introduction of an anti-acetylcholinesterase reversal agent causes:

1 [ACh] is increased to δ[ACh], because acetylcholine hydrolysis at the active site is decreased.
Therefore,

$$NMA = \delta k\Omega[ACh]/[Miva](t) = \delta NMA,$$

an increase of NMA by a factor of δ results in the reversal of the blockade. Subsequent full recovery is still dependent upon biotransformation of the mivacurium. However, if the anticholinesterase also inhibits plasma cholinesterase, the reversal will also

2 Change [Miva](t) to [Miva]'(t), where [Miva](t) and [Miva]'(t) are mivacurium concentrations at the neuromuscular junction, as a function of time without and with the administration of anti-acetylcholinesterase.
Therefore,

$$NMA' = k\Omega[ACh]/[Miva]'(t)$$

When t is small

$$[Miva]'(t) = [Miva](t)$$

$NMA' = \delta NMA$, an increase of activity by δ fold, again a reversal phenomenon.

During the course of recovery, there exists a t at which time [Miva](t) = δ[Miva](t), the anticholinesterase induced recovery slows down such that the activity curve overlaps the spontaneous recovery curve.

$$NMA = \delta k\Omega[ACh]/[Miva]'(t) = \delta k\Omega[ACh]/\delta[Miva](t)$$
$$= \delta k\,[ACh]/[Miva](t) = NMA$$

When t is large, [Miva]'(t) may become larger than δ [Miva](t)

$$NMA' = \delta k\Omega[ACh]/[Miva]'(t) < k\delta\Omega[ACh]/\delta\,[Miva](t) = NMA$$

or $NMA' < NMA$

Therefore, the later phase of recovery is slower than when no reversal agent is given.

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