Neostigmine but not edrophonium prolongs the action of mivacurium

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Purpose: *To examine the influence of anticholinesterase drugs neostigmine and edrophonium (which have different effects on plasma cholinesterase activity) administered for antagonism of neuromuscular block on the duration of action of mivacurium (a neuromuscular blocking drug metabolised by plasma cholinesterase).*

Methods: *This was a randomized study where mivacurium 0.15 mg·kg^{-1} was administered to a control group or after administration of neostigmine 40 μg·kg^{-1} or edrophonium 1 mg·kg^{-1} (n = 10 for each group) administered 10 min earlier for antagonism of atracurium-induced neuromuscular block. Neuromuscular block was measured by stimulation of the ulnar nerve in a train-of-four mode (TOF) and measuring the force of contraction of the adductor pollicis muscle. Baseline plasma cholinesterase activity was estimated before drug administration in all the groups and following anticholinesterase administration.*

Results: *The times to recovery of T_1 (first response in the TOF) to 25 and 90% of control and of the TOF ratio to 0.7 after 0.15 mg·kg^{-1} of mivacurium were 47, 65 and 70 min in the neostigmine group; 25, 36 and 36 min in the edrophonium group and 17, 29 and 27 min respectively in the control group (P < 0.01). The plasma cholinesterase activity (PCHE) after neostigmine decreased from 6596 to 1959 U·L^{-1} (P < 0.001) but there was no change after edrophonium (6140 to 6396 U·L^{-1}).*

Conclusions: *The duration of action of mivacurium is prolonged by previous administration of neostigmine and this is most likely to be due to inhibition of PCHE activity.*

Key word

ANTICHOLINESTERASES: edrophonium, neostigmine;
NEUROMUSCULAR RELAXANTS: atracurium, mivacurium;
PHARMACODYNAMICS: interactions.

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Objectif: *Évaluer l'influence de la néostigmine et de l'édrophonium (qui ont des effets différents sur l'activité de la cholinestérase plasmatique), administrés pour l'antagonisme du bloc neuromusculaire, sur la durée d'action du mivacurium (un myorelaxant métabolisé par la cholinestérase plasmatique).*

Méthodes: *Pour cette étude aléatoire, du mivacurium 0,15 mg·kg^{-1} était administré soit à un groupe contrôle soit après la néostigmine 40 μg·kg^{-1} ou d'édrophonium 1 mg·kg^{-1} (n = 10 pour chaque groupe) administrés dix minutes auparavant pour l'antagonisme du bloc neuromusculaire induit par de l'atracurium. Le bloc neuromusculaire était évalué par stimulation au train-de-quatre (TOF) du nerf cubital et par la mesure de la force de contraction de l'adducteur du pouce. Chez tous les groupes, l'activité initiale de la cholinestérase plasmatique était évaluée avant l'administration du produit et après l'administration de l'anticholinestérasique.*

Résultats: *Les temps requis pour la récupération de T_1 (première réponse au TOF) à 25 et 90% du contrôle et pour un rapport TOF de 0,7 après 0,15 mg·kg^{-1} de mivacurium étaient respectivement de 57, 65 et 70 min dans le groupe néostigmine; 25, 36 et 36 min dans le groupe édrophonium et de 17, 29 et 27 min dans le groupe néostigmine; 25, 36 et 36 min dans le groupe édrophonium et de 17, 29 et 27 min dans le groupe contrôle (P < 0,01). L'activité de la cholinestérase plasmatique (PCHE) après néostigmine diminuait de 6596 à 1959 U·L^{-1} (P < 0,001) mais il n'y avait pas de changement après édrophonium (6140 à 6396 U·L^{-1}).*

Conclusion: *La durée d'action du mivacurium est prolongée par l'administration préalable de néostigmine, ce qui est vraisemblablement dû à l'inhibition de l'activité de la PCHE.*

Mivacurium is a short acting non-depolarising neuromuscular relaxant metabolized by plasma cholinesterase (PCHE).[1] The duration of action of mivacurium is inversely related to PCHE activity.[2] Previous studies have shown that neostigmine but not edrophonium is associated with marked inhibition of PCHE activity and this can be associated with a prolongation of the effect of succinylcholine in both experimental and clinical situations.[3–6] Thus, it is possible that the duration of action

of mivacurium may be prolonged by previous administration of neostigmine but not of edrophonium. The present study was undertaken to examine the effect of these anticholinesterase agents on the neuromuscular effects of mivacurium.

Methods

Thirty ASA physical status I or II adult patients between the ages of 18 and 65 yr were included in the study with their informed consent and approval of the Research Ethics Committee. Patients with any neuromuscular disorder, taking medication known to interact with neuromuscular blocking drugs, more than 25% below or above ideal weight were excluded. They were premedicated with 10–20 mg temazepam po, and anaesthetized with 2–3 $\mu g \cdot kg^{-1}$ fentanyl, 4–5 $mg \cdot kg^{-1}$ thiopentone, halothane 0.75% (end-tidal) in 66% nitrous oxide and oxygen, and further increments of fentanyl as required. Continuous ECG, non-invasive blood pressure, end-tidal carbon dioxide concentration and oxygen saturation were monitored. Ventilation was adjusted to maintain normocapnia and the temperature of the hand was kept >32°C.

The ulnar nerve was stimulated at the wrist with supramaximal stimuli of 0.2 msec duration in a train-of-four (TOF) mode at 2 Hz every 12 sec and the force of contraction of the adductor pollicis muscle recorded using a force displacement transducer and a neuromuscular function analyzer (Myograph 2000, Biometer Ltd, Denmark). The control responses were allowed to stabilize for a period of 10 min.

Ten patients each were randomly allocated to one of the three groups. The patients in the first two groups received 0.4 $mg \cdot kg^{-1}$ atracurium. The patients in these two groups were given 40 $\mu g \cdot kg^{-1}$ neostigmine (with 10 $\mu g \cdot kg^{-1}$ of glycopyrrolate) or 1 $mg \cdot kg^{-1}$ edrophonium (with 10 $\mu g \cdot kg^{-1}$ atropine) when the T_1 (the first response in the TOF) had recovered to 25% of control. These are the commonly used dosage combinations of the two anticholinesterase and anticholinergic drugs. Mivacurium 150 $\mu g \cdot kg^{-1}$ was then administered 10 min after the reversal agent at which time the T_1 was >90% of control and the TOF ratio close to 0.9. The third group received only 150 $\mu g \cdot kg^{-1}$ mivacurium after the initial stabilization of the neuromuscular responses and served as a control group.

The times to onset of maximum block, and to the recovery of T_1 to 25 and 90% of control and of the TOF ratio of 0.7 following mivacurium administration were recorded. Recovery index was calculated as the time taken for the recovery of T_1 from 25 to 75%.

Venous blood samples were obtained from all patients at the time of induction of anaesthesia and at 5 and 10 min after administration of the anticholinesterase but before the administration of mivacurium agents. For estimation of PCHE activity, plasma was separated within one hour of collection and stored at −20°C. Analysis of PCHE activity was carried out using a Cholinesterase kit (Sigma) run on a Beckman Synchron CX5 spectrophotometer using butyrylcholine as the substrate. The values in phenotypically normal individuals ranged between 3000 and 9000 $U \cdot L^{-1}$. The coefficient of variability of the estimation was <5%.

The results were subjected to analysis of variance for comparison of the neuromuscular data among groups and to repeated measures analysis of variance for PCHE activity followed by t tests with Bonferroni correction if analysis of variance showed significant differences.

TABLE I Demographic data (mean ± SD)

	n	*Age (yr)*	*Sex (M/F)*	*Weight (kg)*	*Height (cm)*
Control	10	38 ± 15.1	5/5	63 ± 11.1	167 ± 8.1
Edrophonium	10	39 ± 13.3	5/5	73 ± 12.1	173 ± 7.6
Neostigmine	10	46 ± 13.9	6/4	68 ± 8.5	168 ± 6.2

Results

The groups were comparable with respect to age, weight and height (Table I). The onsets and durations of action of mivacurium are given in Table II. The onset of action of mivacurium in the neostigmine and edrophonium groups was shorter (77 ± 16.7 and 70 ± 7.9 sec respectively) than 109 ± 26.8 sec in the control group ($P < 0.05$). The time to recovery of T_1 to 25% (clinical duration) of mivacurium was longer in the neostigmine group than in the edrophonium and control groups (47 ± 14.9, 25 ± 4.0, and 17 ± 4.0 min respectively; $P < 0.01$). The same was true for the recovery of T_1 to 90% (65 ± 9.4, 36 ± 7.3, and 29 ± 9.9 min respectively; $P < 0.01$); recovery of the TOF ratio to 0.7 (70 ± 15.7, 36 ± 3.6, and 27 ± 6.5 min respectively; $P < 0.01$), and the recovery Index (17.6 ± 8.8, 8.1 ± 2.2, and 8.0 ± 4.6 min respectively; $P < 0.01$).

The baseline PCHE concentrations were 7252 ± 1533, 6140 ± 1733 and 6596 ± 1734 $U \cdot L^{-1}$ in the control, edrophonium and the neostigmine groups respectively (Table III); these were not different. The levels were decreased markedly to 1959 ± 1466 and 2374 ± 1588 $U \cdot L^{-1}$ at 5 and 10 min in the neostigmine group ($P < 0.001$) but the changes in the edrophonium group were small and not significant (levels of 6301 ± 1406 and 6396 ± 1415 $U \cdot L^{-1}$ at 5 and 10 min respectively).

Discussion

The present study was undertaken to examine the interaction between anticholinesterase agents and mivacuri-

TABLE II Onset and recovery times of mivacurium 150 $\mu g \cdot kg^{-1}$ with or without previous administration of anticholinesterase drugs (Mean ± SD)).

	Control (n = 10)	*Edrophonium (n = 10)*	*Neostigmine (n = 10)*
Onset (sec)	109 ± 26.8	70 ± 7.9*	77 ± 16.7*
Time (min) to recovery of			
– T_1 to 25%	17 ± 4.0	25 ± 4.0	47 ± 14.9†
– T_1 to 90%	29 ± 9.9	36 ± 7.3[a]	65 ± 9.4[b]†
– TOF ratio of 0.7	27 ± 6.5	36 ± 3.6	70 ± 15.7†
Recovery index (min)	8.0 ± 4.6	8.1 ± 2.2[b]	17.6 ± 8.8†

$N = 10$ for each group except $a = 8$ and $b = 9$.
*$P < 0.05$ compared with control group; †$P < 0.01$ compared with other two groups.

TABLE III Plasma cholinesterase activity in $U \cdot L^{-1}$ (Mean ± SD).

	Control	*Edrophonium*	*Neostigmine*
Baseline	7252 ± 1533	6140 ± 1733	6596 ± 1733
5 min		6301 ± 1406	1959 ± 1465*
10 min		6396 ± 1414	2374 ± 1587*

*$P < 0.001$ compared with baseline values and values in the edrophonium group.

um and showed that the duration of action of mivacurium was prolonged by previous administration of neostigmine.

Neostigmine acts as a decurarizing agent by virtue of its antiacetylcholinesterase activity but the present and previous studies have shown inhibition of plasma cholinesterase activity as well.[3,6] Reduction in plasma cholinesterase activity of the extent observed in the present study results in a prolongation of the action of succinylcholine.[6] It has previously been shown that the duration of action of mivacurium is inversely related to PCHE activity in phenotypically normal subjects.[2] It is therefore likely that this reduction in PCHE activity is the reason for the prolongation of the action of mivacurium in the present study. The choice of atracurium as the initial muscle relaxant was on the basis of minimal effects of this agent on PCHE activity.[7]

In the present study, the increase in the duration of action of mivacurium was about two and a half times longer after neostigmine than in the control group. The increase in the edrophonium group was relatively small and statistically insignificant consistent with little effect on PCHE activity due to edrophonium. It is possible that prolongation of some of this effect of mivacurium may be due to the residual effect of atracurium. This could also account for its somewhat faster onset of action in the two study groups than in the control group. While it is a possible reason for the faster onset and some increase in the duration of action of mivacurium, it is unlilely to be the predominant reason for prolongation of its effect. The duration of action of mivacurium in that case would be similar in the edrophonium and neostigmine groups. However, the duration of action of mivacurium in our study in the edrophonium group was similar to that in the control group. The marked prolongation of effect of mivacurium in the neostigmine group would therefore appear to be mainly related to a marked reduction in the PCHE activity in this group. The faster onset of the effect of mivacurium in the two study groups could still have been due to the residual effect of atracurium.

The findings of the present study are at variance with the findings of Fleming and Lewis who showed that previous administration of edrophonium, pyridostigmine or neostigmine did not increase the duration of action of mivacurium in rats.[8] However, this may be due to a species difference as the PCHE activity in rats is much lower than in humans.[9] These authors did not measure the PCHE activity in their study. In addition the animals in their study received mivacurium both before and after anticholinesterases, thus receiving a much larger dose of mivacurium.

In conclusion, neostigmine given for reversal of block results in a marked prolongation of subsequently administered mivacurium due to a reduction in PCHE activity. The PCHE activity following neostigmine administration may remain suppressed for up to four hours although the effects are most pronounced for the first 30–45 min.[3] It is therefore suggested that mivacurium be avoided or used in a smaller dose if the use of a muscle relaxant is contemplated soon after the reversal of a previous block with neostigmine.

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