Priming with anticholinesterases - the effect of different priming doses of edrophonium

Mohamed Naguib MB BCH MSC FFARCSI,
Mohamed Abdulatif MB BCH MSC

The effect of different priming doses of edrophonium were studied in 77 patients divided into seven groups (n = 11 in each). Edrophonium 1.0 mg·kg^{-1} was administered either in a single bolus dose (Group I; controls) or in an initial dose of 0.05, 0.1, 0.15, 0.2, 0.25 or 0.3 mg·kg^{-1} followed one minute later by the remainder of the 1.0 mg·kg^{-1} dose in Groups II to VII respectively. Reversal was attempted at ten per cent spontaneous recovery of twitch height (T1) from atracurium-induced neuromuscular blockade. Increasing the size of the priming dose from 0.05 to 0.2 mg·kg^{-1} resulted in a stepwise increase ($p < 0.05$) in recovery of T1 and train-of-four (TOF) ratio. Higher priming doses (0.25 and 0.3 mg·kg^{-1}) were not associated with further improvement in T1 and TOF recovery. Reversal time, that is the time taken from the first injection of edrophonium until the TOF ratio value had reached 0.75 was significantly faster ($p < 0.01$) following priming with edrophonium 0.2 mg·kg^{-1} (Group V) when compared to Groups I, II, III, IV and VI. Reversal times were also significantly faster in Groups IV and VI when compared to the control group.

It is concluded that 0.2 mg·kg^{-1} appears to be the optimal priming dose for administration of edrophonium in divided doses.

Key words

ANTAGONISTS, NEUROMUSCULAR RELAXANTS: edrophonium; PHARMACODYNAMICS: priming principle; NEUROMUSCULAR RELAXANTS: atracurium; NEUROMUSCULAR TRANSMISSION: train-of-four.

From the Department of Anesthesiology, King Faisal University, King Fahd Hospital, Al-Khobar, Saudi Arabia.

Address correspondence to: Dr. Mohamed Naguib, King Faisal University, King Fahd Hospital, P.O. Box 2208, Al-Khobar 31952, Saudi Arabia.

We reported that divided administration of neostigmine or edrophonium hastens the recovery of atracurium-induced neuromuscular blockade as compared to a single bolus administration of the antagonist.[1,2] We also demonstrated that a one minute priming interval and the administration of edrophonium in divided doses resulted in the fastest recovery rate following antagonism of atracurium induced neuromuscular blockade as compared to different combinations of neostigmine and edrophonium at different intervals.[3]

This study was undertaken to investigate the reversal characteristics following different priming doses of edrophonium.

Methods

After institutional approval, 77 ASA physical status I or II adult patients undergoing minor elective procedures were studied. All patients were free of neuromuscular, renal or hepatic disease and were not taking any drugs known to interfere with neuromuscular function. Informed consent was obtained. All patients were premedicated with diazepam 0.15 mg·kg^{-1} PO 90 minutes preoperatively.

An intravenous infusion of lactated Ringer's solution in five per cent dextrose was established prior to induction. The ECG and nasopharyngeal temperature were monitored continuously by a Medishield® M1 monitor. Blood pressure was measured every five minutes by an electronic oscillotonometer (Dinamap®).

In all patients, anaesthesia was induced with fentanyl 2.0 μg·kg^{-1} thiopentone 5.0 mg·kg^{-1} and was maintained with 70 per cent nitrous oxide in oxygen and halothane (0.5–1 per cent). Ventilation was adjusted to maintain normocapnia and end-tidal CO_2 was monitored by a Datex infra-red CO_2 analyzer.

The ulnar nerve was stimulated at the wrist with square wave supramaximal stimuli of 0.2 ms duration, delivered in a train-of-four (TOF) sequence at 2 Hz every ten seconds, using a Myotest® peripheral nerve stimulator (Biometer). The resultant contraction of adductor pollicis was recorded using a force displacement transducer and

TABLE I Demographic data (n = 11 in each group). Median values ± standard errors

Group	Age (years)	Weight (kg)	Sex M/F
I*	30 ± 1.7	67 ± 2.9	6/5
II	32 ± 3.2	63 ± 6.1	7/4
III	34 ± 4.3	60 ± 6.1	6/5
IV	34 ± 5.5	67 ± 3.8	6/5
V	28 ± 4	60 ± 3.2	7/4
VI	31 ± 4	60 ± 4	7/4
VII	30 ± 1.4	68 ± 2.3	6/5

*Control group.

neuromuscular function analyzer (Myograph 2000 Biometer).[4] Preload tension on the thumb was maintained at 300 throughout the investigation.

After stablization of twitch recording, atracurium 0.5 $mg \cdot kg^{-1}$ was administered and tracheal intubation was performed at maximum block. Patients were excluded from the study if additional doses of atracurium were given.

At the end of surgery, when spontaneous recovery had begun and the first twitch (T1) of the TOF returned to ten per cent of the control value, patients were assigned randomly to one of seven groups (n = 11 in each). The same total dose of edrophonium 1.0 $mg \cdot kg^{-1}$, was given to all patients. In Group I (controls) edrophonium was administered as a single bolus dose. In Groups II to VII, edrophonium was administered as an initial dose of 0.05, 0.01, 0.15, 0.20, 0.25 or 0.30 $mg \cdot kg^{-1}$ respectively followed one minute later by the rest of the dose. In all patients atropine 0.02 $mg \cdot kg^{-1}$ was administered before the edrophonium. Patients continue to inhale 70 per cent nitrous oxide in oxygen and 0.5–1 per cent halothane until all measurements were complete. Antagonism of block was considered adequate when a TOF ratio (the amplitude of the fourth to the first evoked response, T4/T1) of 0.75 was attained.[5] Further assessment of the patients was carried out in the Recovery Room for 60 minutes using clinical criteria such as ability to open eyes, cough and sustain a head lift.

The following parameters were calculated: (a) T1 and TOF ratio just before the administration of the second dose of the antagonist; (b) time for the twitch height (T1) to recover from 25 to 75 per cent of control (recovery index); and (c) reversal time, was the time taken from the first injection of the antagonist until the TOF ratio value had reached 0.75.

Data analysis

Statistical analysis was performed by the BMDP package.[6] Data for the patients were compared by Kruskal-Wallis one way analysis of variance. The two-tailed Mann-Whitney U-test was used for comparison between groups; a value of $p < 0.05$ was considered to be significant.

Results

All results are expressed as the median ± standard error of the median. There was no significant difference among the seven groups with respect to age, body weight and sex distribution (Table I).

Maximum effect of the priming dose

Increasing the size of the priming dose of edrophonium from 0.05 $mg \cdot kg^{-1}$ to 0.3 $mg \cdot kg^{-1}$ resulted in a greater recovery of T1 and TOF ratio ($p < 0.05$) in Groups V to VII each as compared with Group II, III and IV (Table II). In addition, the degree of recovery of the twitch height (T1; per cent of control value) was significantly greater in Groups III and IV each as compared with Group II and Groups II and III respectively. Also, TOF ratios were significantly greater in Groups III and IV each as compared with Group II (Table II).

TOF ratios at 3 min from the first administration of edrophonium are shown in Table II. The ratio was significantly higher ($p < 0.01$) in Group V when compared with groups I, II, III, IV and VI.

Recovery index and reversal time

There was no significant difference in the recovery indices among the groups whether edrophonium was administered as a single bolus (Group I) or in divided doses (Groups II to VII).

Adequate antagonism (a TOF ratio of 0.75) was obtained in all patients. Reversal time was significantly faster ($p = 0.0094$ or less) in Group V when compared to Groups I, II, III, IV and VI (Table II). Reversal times were also shorter ($p = 0.02$) in Groups IV and VI when compared to the control group (Group I). Reversal time in Group VII was not significantly different from the other groups.

Discussion

Recent studies have demonstrated that edrophonium in adequate doses can produce a rapid onset of antagonism of nondepolarizing muscle relaxants with a duration of action equivalent to that of neostigmine.[7–14] Nevertheless, several studies demonstrated that edrophonium in doses between 0.5–0.75 $mg \cdot kg^{-1}$ cannot be relied upon to antagonize relatively deep blocks produced by pancuronium, atracurium and vecuronium.[7,12,14–17] Antagonism of relatively profound degrees of blockade may be difficult with edrophonium.[8,13–17] Rupp *et al.*[15] suggested that the edrophonium dose should be at least 1.0 $mg \cdot kg^{-1}$ in order to achieve antagonism as rapid as

TABLE II Priming dose, priming interval, first twitch (T1), train-of-four (TOF) ratio, recovery index and reversal time. Median values ± standard errors

Group	Priming dose ($mg \cdot kg^{-1}$)	Priming interval (min)	Maximum effect of the priming dose* T1 (% of control)	Maximum effect of the priming dose* TOF ratio	TOF ratio at 3 min.†	Recovery index (sec)	Reversal time (sec)
I	—	—	—	—	0.54 ± 0.04	95 ± 66.4	675 ± 77.9
II	0.05	1	30 ± 2.9	0.1 ± 0.04	0.63 ± 0.03	70 ± 5.8	380 ± 114
III	0.10	1	40 ± 3.5§	0.17 ± 0.03§	0.61 ± 0.05	75 ± 11.5	435 ± 165.9
IV	0.15	1	52 ± 3.2§	0.25 ± 0.06§	0.62 ± 0.03	70 ± 7.2	390 ± 86.6**
V	0.20	1	60 ± 4.6¶	0.47 ± 0.07¶	0.75 ± 0.03‡	75 ± 31.8	160 ± 54.8‖
VI	0.25	1	60 ± 8.6¶	0.36 ± 0.03¶	0.60 ± 0.03	50 ± 14.4	440 ± 31.8**
VII	0.30	1	70 ± 12.9¶	0.37 ± 0.05¶	0.61 ± 0.08	50 ± 24.5	500 ± 155.9

*Just before the administration of the second dose of edrophonium.
†From the first administration of edrophonium.
‡$p < 0.01$ compared with Group I, II, III, IV and VI.
§$p < 0.05$ as compared with Group II.
¶$p < 0.05$ as compared with Group II, III and IV.
‖Reversal time significantly faster ($p = 0.0094$ or less) in Group V when compared with Groups I, II, III, IV and VI.
**Reversal times significantly faster ($p = 0.02$) in Groups IV and VI when compared with control group (Group I).

neostigmine 0.04 $mg \cdot kg^{-1}$ when twitch height is 2–10 per cent of control.

In this study, reversal from 90 per cent twitch depression was achieved within 10 minutes following administration of a single bolus of edrophonium 1.0 $mg \cdot kg^{-1}$. It might be implied that larger doses of edrophonium resulted in a sufficient concentration of drug to be present for inhibition of acetylcholinesterase enzyme to be maintained.

The hypothesis that administration of anticholinesterases in divided doses will markedly shorten the reversal time of atracurium was clearly demonstrated in previous studies.[1–3]

In priming studies of non-depolarizing muscle relaxants, increasing the size of the priming dose resulted in increasing fade of the TOF ratio, as well as an acceleration of the onset of paralysis following the administration of the second dose.[18,19] This observation is consistent with a larger "margin of safety" at the neuromuscular junction.[20] In this study, increasing the size of the priming dose of edrophonium from 0.05 $mg \cdot kg^{-1}$ to 0.30 $mg \cdot kg^{-1}$ resulted in stepwise increase ($p < 0.05$) in recovery of T1 and TOF ratio with each increase in the dose up to 0.2 $mg \cdot kg^{-1}$. This effect is also consistent with the margin of safety in the inhibition of the acetylcholinesterase enzyme, as described by Barber *et al.*[21] However, no further improvement in the recovery T1 and TOF was observed with higher doses of edrophonium (0.25 and 0.3 $mg \cdot kg^{-1}$).

In the present study, following administration of the antagonist in divided doses, reversal time was significantly faster following priming with edrophonium 0.2 $mg \cdot kg^{-1}$ (Group V) when compared to Groups I, II, III, IV and VI. The improvement in the reversal time seen with a priming dose of 0.2 $mg \cdot kg^{-1}$ could be attributed to the larger TOF ratio present before the second dose was given. Reversal times were also significantly faster following priming with 0.15 $mg \cdot kg^{-1}$ and 0.25 $mg \cdot kg^{-1}$ in groups IV and VI respectively, as compared to the control group (Group I). This might indicate that priming with smaller doses of edrophonium (0.05 or 0.1 $mg \cdot kg^{-1}$) was not sufficient to bring about a reduction in the "margin of safety" in enzyme inhibition. Therefore, no significant acceleration of reversal was observed in the latter groups. On the other hand, increasing the priming dose of edrophonium to 0.3 $mg \cdot kg^{-1}$ was not associated with any significant shortening of the reversal time. This is difficult to explain. Nevertheless, it could be assumed that the size of the two doses (priming and second dose) used in the latter group (Group VII) was not optimal and might have exerted a curare-like action which opposed any further facilitation of transmission. This effect has been described following the administration of high doses of anticholinesterases.[22] Payne *et al.*[23] reported that the administration of a second dose of 2.5 neostigmine caused reduction in the peak tetanic contraction and tetanic fade. In contrast, Fox *et al.*[24] failed to demonstrate any increase in fade in the TOF ratio after administration of two doses of 2.5 mg neostigmine separated by a 2-min interval. However, the results of these studies[23,24] are difficult to compare because of different anaesthetic, stimulating and recording techniques used. Foldes *et al.*[25] reported that the antagonist potency of anticholinesterases and the maximal recovery after the use of the optimal concentrations of these antagonists was less in the preparations stimulated with short train of tetani than in those stimulated with single impulses.

In this study as well as the previous reports[1-3] we tried to identify the components of an ideal priming combination (the priming dose, the priming interval, and the second antagonist). If we combine the results of these studies it would appear that administration of edrophonium in divided doses (0.2 $mg \cdot kg^{-1}$ followed by 0.8 $mg \cdot kg^{-1}$) with an interval of one minute between the doses is the optimal combination of those studied.

In conclusion, we demonstrated that the reversal of atracurium-induced neuromuscular blockade could be accelerated by divided administration of edrophonium. Priming doses in range of 0.15 to 0.2 $mg \cdot kg^{-1}$, followed one minute later by the remainder of the 1.0 $mg \cdot kg^{-1}$ dose resulted in a significant acceleration in the reversal time as compared to a single bolus administration of the antagonist. Acceleration in the reversal time, however, was more marked following priming with the 0.2 $mg \cdot kg^{-1}$ dose. Therefore, for rapid antagonism of deep atracurium paralysis (at 90 per cent depression of twitch height), we recommend the administration of edrophonium 0.2 $mg \cdot kg^{-1}$ as the priming dose, followed by 0.8 $mg \cdot kg^{-1}$, with an interval (priming interval) of one minute between the doses.

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Résumé

L'effet de différentes doses d'amorce d'édrophonium a été étudié chez 77 patients divisés en sept groupes (n = 11). L'édrophonium 1.0 mg·kg^{-1} a été administré soit en une dose unique (Groupe I, contrôle) ou en une dose initiale de 0.05, 0.1, 0.15, 0.2, 0.25 ou 0.3 mg·kg^{-1} suivi une minute plus tard par le restant de la dose de 1.0 mg·kg^{-1} pour les Groupes II à VII. L'antagonisme a été tenté aprés une récupération spontanée à dix pour cent de la hauteur de twitch (T1) aprés un bloc neuromusculaire induit par l'atracurium. L'augmentation de la dose d'amorce de 0.05 à 0.2 mg·kg^{-1} a produit une augmentation de plus en plus accrue ($p < 0.05$) dans la récupération de T1 et du rapport de l'ondée-de-quatre (TOF). La plus grande dose d'amorce (0.25 et 0.3 mg·kg^{-1}) n'était pas associée avec de plus grandes améliorations dans la récupération de T1 et TOF. Le temps d'antagonisme, qui représente le temps du début de la première injection d'édrophonium jusqu'à l'obtention d'un rapport de TOF de 0.75 était significativement plus rapide ($p < 0.01$) aprés la dose d'amorce d'édrophonium de 0.2 mg·kg^{-1} Groupe V) en comparaison Groupe I, II, III, IV et VI. Les temps d'antagonisation étaient aussi significativement plus rapides dans les groupes IV et VI comparativement groupe contrôle. On conclut que la dose de 0.1 mg·kg^{-1} apparaît optimale comme dose d'amorce pour l'administration de l'édrophonium en doses fractionnées.