Neostigmine antagonism of succinylcholine phase II block: a comparison with pancuronium

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To assess the efficacy of neostigmine antagonism of succinylcholine phase II block, succinylcholine infusions were given to 17 patients for durations varying from 44 to 192 minutes. A control group (17 patients) received a pancuronium infusion for similar times. Ninety per cent neuromuscular block was maintained in these two groups by adjustment of the infusion rates and, in a third group, with intermittent doses of pancuronium. Neuromuscular transmission was monitored with train-of-four stimulation every 12 seconds and anaesthesia was maintained with N₂O-O₂-enflurane. Ten minutes after the infusion was stopped, atropine and neostigmine were given to all patients who received pancuronium and to 11 patients in the succinylcholine group whose train-of-four ratio (T₄/T₁) was less than 0.7. During the subsequent 15 minutes, recovery was more rapid in the succinylcholine group than in either the pancuronium-infusion or pancuronium-bolus groups. It is concluded that succinylcholine-induced phase II block can be safely and rapidly antagonized with neostigmine.

Key words

ANTAGONISTS: neostigmine; NEUROMUSCULAR RELAXANTS: succinylcholine, pancuronium, phase II block.

Prolonged administration of succinylcholine is associated with a neuromuscular block (NMB) which changes from depolarizing to non-depolarizing (phase II) in character.^{1,2} The change occurs in association with increasing dose and duration of administration of succinylcholine. Reversal of phase II block with anticholinesterases is well established.^{3,4} However, the rate of recovery of phase II block has not been compared with the recovery of a non-depolarizing relaxant after each has been antagonized with neostigmine.

In the present study, succinylcholine or pancuronium was given to maintain clinically adequate levels of NMB for varying times (44–192 minutes) as required in routine anaesthetic practice. The recovery of neuromuscular function, spontaneously and after neostigmine, was compared for the two relaxants.

Methods

The protocol was approved by the hospital Ethics Committee. After informed consent had been obtained, 51 adult patients, ASA physical status I or II, without known or suspected neuromuscular, hepatic or renal disease and undergoing a variety of surgical procedures were studied. They were premedicated with a narcotic with an antimuscarinic agent and/or a benzodiazepine.

Anaesthesia was induced with thiopentone (3–5 mg·kg⁻¹) and maintained with nitrous oxide (70 per cent in oxygen) and enflurane (one to two per cent). Blood pressure and the electrocardiogram were recorded.

Neuromuscular transmission was monitored using the method described by Ali *et al.*⁵ The ulnar nerve was stimulated supramaximally with subcutaneous needle electrodes at the elbow. Four square wave

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TABLE

	Sex	Age (years)	Weight (kg)	Infusion time (min)	Total dose (mg)
Succinylcholine	11 M 6 F	41.3 $\pm$ 3.9	67.8 $\pm$ 2.8	104.5 $\pm$ 10.0	739.9 $\pm$ 73.9
Pancuronium infusion	5 M 12 F	40.4 $\pm$ 3.9	61.9 $\pm$ 3.0	100.6 $\pm$ 9.8	4.9 $\pm$ 0.3
Pancuronium bolus	10 M 7 F	48.9 $\pm$ 3.8	62.6 $\pm$ 3.9	103.8 $\pm$ 9.5	5.25 $\pm$ 0.5

impulses of 0.2 ms duration and 2 Hz frequency were administered every 12 seconds using a Grass S48 stimulator and SIU5 isolation unit. The hand and forearm were immobilized in a splint. The force of contraction of the adductor pollicis muscle was measured with a Grass FT10 force displacement transducer and the response recorded on a Grass Polygraph pen and ink recorder. Phase II block was defined as a train-of-four ratio (T4/T1) of less than 0.5. The skin temperature over the adductor pollicis was monitored and maintained above 32°C. Patients were allocated randomly to three equal size groups.

After induction of anaesthesia, control twitch measurements were made when a stable baseline had been obtained, i.e., when three consecutive trains of stimulations produced identical responses. Then infusions of either succinylcholine, 0.4 per cent in five per cent dextrose (Group I), or pancuronium, 0.004 per cent in five per cent dextrose (Group II), were given via an IMED constant infusion pump at a rate to maintain 90 per cent block, i.e., the force of the first twitch was ten per cent of control. In Group III NMB was maintained with intermittent boluses of pancuronium 0.01 mg·kg⁻¹, given whenever the force of the first twitch returned to ten per cent control. The trachea was intubated in all patients when NMB first exceeded 90 per cent. Then they were ventilated to normocapnia as assessed by end-tidal carbon dioxide measurement using a Hewlett-Packard HP capnograph.

There were 17 patients in each group, matched for duration of NMB, which ranged from 44–192 minutes. After the cessation of the infusion, the neuromuscular junction was allowed to recover for ten minutes when atropine, 0.017 mg·kg⁻¹, and neostigmine, 0.036 mg·kg⁻¹, were given to all patients whose T4/T1 was less than 0.7. This was

necessary in all patients who had received pancuronium and in 11 who had received succinylcholine. An identical recovery time was allowed in those patients who had received pancuronium by bolus injection.

Mean values are presented with the standard error of the mean as the index of dispersion. Where applicable, analysis of variance (ANOVA) and Student's *t* tests (STT) were used, the null hypothesis being rejected when *p* < 0.05.

Results

There were no significant differences in the mean ages, weights or infusion times between the three groups of patients (Table) (ANOVA).

The infusion requirement in the succinylcholine group to maintain constant NMB increased by 80 per cent (tachyphylaxis) during the first 99 minutes as phase II block developed. Pancuronium maintenance requirements were approximately 1 µg·kg⁻¹·min⁻¹ in both the infusion and the intermittent bolus groups, and did not change with time. Spontaneous and neostigmine-induced recovery for the first twitch and train-of-four ratio were very similar in both pancuronium groups (Figures 1 and 2).

Although phase II block developed in 16 of 17 patients receiving succinylcholine, spontaneous recovery ten minutes after stopping the infusions was greater in the succinylcholine group (Group I) than in the pancuronium group (Group II) (*p* < 0.001, STT) (Figures 3 and 4). Six patients in the succinylcholine group recovered to a T4/T1 of more than 0.7 in ten minutes and did not require neostigmine. The remaining 11 patients received neostigmine, after which the rate of recovery increased in all (Figures 3 and 4). Residual block was markedly less in this succinylcholine sub-group than in the pancuronium group, at all measurement times up to 25

FIGURE 1 Force of the first twitch of the train-of-four (T_1) expressed as a percentage of initial value, versus time after beginning of spontaneous recovery, in 17 patients receiving pancuronium as an infusion and 17 others receiving pancuronium in intermittent bolus form. Time zero is when the infusion was stopped (infusion group), or at ten per cent spontaneous recovery after the last bolus dose (bolus group). Neostigmine ($2.5 \text{ mg} \cdot 70 \text{ kg}^{-1}$) given at ten minutes.

minutes after stopping the infusion ($p < 0.001$, STT). Furthermore, the first twitch tension commonly exceeded its control value (mean 140 per cent at 20 minutes), after a succinylcholine infusion. This did not occur after pancuronium.

Discussion

The management of patients recovering from prolonged succinylcholine infusions is controversial. Anticholinesterases, such as neostigmine, inhibit plasma cholinesterase⁶ and their use potentiates and prolongs phase I (depolarizing) block.^{6,7} Although some authors have cautioned against the use of anticholinesterases in phase II block,⁷ several studies have documented the ability of neostigmine or edrophonium to antagonize a phase II block.^{3,4,8}

The aim of this study was to assess the efficacy of neostigmine in antagonizing phase II blockade after

a prolonged infusion, and to compare the results with the antagonism of the same degree of block produced by pancuronium infusion of similar duration. Because pancuronium is usually given intermittently, it was necessary to establish that recovery after an infusion was the same in time course and extent in both the infusion and intermittent bolus cases (Figures 1 and 2).

The net result following cessation of administration of neuromuscular blocking drugs is the sum of spontaneous recovery and antagonist-assisted recovery. In the present study the spontaneous recovery in patients who had received succinylcholine, despite the development of phase II block, was much greater than in those who had received pancuronium. The addition of neostigmine accelerated recovery in both groups so that up to 25 minutes after stopping the infusions the net recov-

FIGURE 2 Train-of-four ratio (T_4/T_1) versus time after beginning of spontaneous recovery. Same patients as in Figure 1.

ery was greater in the succinylcholine than pancuronium infusion groups.

All patients in the succinylcholine group who received neostigmine showed an acceleration of their recovery, even if their T_4/T_1 was close to 0.7. Lee³ reported either no change or potentiation of the block with edrophonium when T_4/T_1 was greater than 0.4. The discrepancy is probably not due to the different anticholinesterase, but rather to the duration of succinylcholine administration. Lee used edrophonium soon after short infusions of succinylcholine, so that a T_4/T_1 of 0.7 for instance, represented phase I block. In the present study, phase II block was clearly established (T_4/T_1 of zero) during the infusion in all patients who received neostigmine so that a T_4/T_1 of 0.7 after ten minutes of spontaneous recovery should be interpreted as recovery of a phase II block rather than a phase I block.

The potentiation of T_1 beyond control levels in the succinylcholine group (Figure 3) has been described in animal studies.⁹ The underlying mechanisms are not known and this finding deserves further investigation in man.

The levels of neuromuscular blockade achieved and maintained in this study (90 per cent) are in excess of that usually required clinically. Therefore, in clinical practice reversal would probably proceed more rapidly after both succinylcholine and pancuronium. However, it can be concluded that if 90 per cent NMB is maintained for up to three hours with infusions of either succinylcholine or pancuronium, then neuromuscular function is likely to return to normal more rapidly with succinylcholine than pancuronium if neostigmine is used to antagonize any succinylcholine-induced phase II block.

FIGURE 3 Force of the first twitch of the train-of-four (T1), expressed as a percentage of initial value, versus time after stopping the relaxant infusion, in 17 patients receiving pancuronium, and in 11 patients receiving succinylcholine who were given neostigmine. Six patients who were given succinylcholine did not receive neostigmine because spontaneous recovery was sufficient.

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FIGURE 4 Train-of-four ratio (T_4/T_1) versus time after stopping the relaxant infusion. Same patients as in Figure 3.

Résumé

Afin d'évaluer l'efficacité de la néostigmine dans l'antagonisme du bloc de phase II produit par la succinylcholine, on a administré des perfusions de succinylcholine à 17 patients pendant 44 à 192 minutes. Un groupe témoin (17 patients) a reçu du pancuronium pour des durées comparables. Chez ces deux groupes, on a maintenu un bloc neuromusculaire de 90 pour cent en ajustant la vitesse de perfusion, tandis que chez un troisième groupe, on a atteint le même but par des doses intermittentes de pancuronium. On a utilisé le train de quatre stimulations (train-of-four) toutes les 12 secondes. L'anesthésie était entretenue à l'aide de protoxyde d'azote, d'oxygène et d'enflurane. Dix minutes après la fin de la perfusion, on a administré de l'atropine et de la néostigmine à tous les patients qui ont reçu du pancuronium et aux 11 patients qui ont reçu de la succinylcholine et dont le ratio de la quatrième à la première contraction (T_4/T_1) était inférieur à 0.7. Pendant les 15 minutes suivantes, les patients qui avaient reçu de la

succinylcholine ont récupéré plus rapidement que les autres. On peut donc antagoniser le bloc de phase II produit par la succinylcholine de façon sûre et rapide avec de la néostigmine.