Onset of pancuronium and d-tubocurarine blockade with priming

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The synergistic effect of pancuronium bromide (PCB) and d-tubocurarine (DTC) on the onset time of neuromuscular blockade was tested in 108 ASA physical status I and II adults anaesthetized with thiopentone, nitrous oxide and halothane. Either saline or a small (priming) dose (DTC, 0.04 mg·kg^{-1}, or PCB, 0.007 mg·kg^{-1}) was administered 3 min before a paralyzing dose of either DTC or PCB. The total dose of relaxant was equivalent to DTC, 0.4 mg·kg^{-1}, or PCB, 0.07 mg·kg^{-1}. Neuromuscular activity was measured using train-of-four stimulation applied every 12 s. Time to 50 per cent first twitch blockade was 63 ± 4.6 s (mean ± SEM) with DTC and 88 ± 5.2 s with PCB ($p < 0.002$). Times to 90 per cent blockade were not different between the two drugs (161 ± 20 s and 141 ± 21 s respectively). Priming a DTC blockade with either DTC or PCB or priming a PCB blockade with PCB produced an acceleration of less than 10 s at all levels of blockade. Compared with PCB alone, priming PCB blockade with DTC reduced the time to 50 per cent blockade to 71 ± 4.5 s ($p < 0.02$) and to 90 per cent blockade to 111 ± 8 s ($p < 0.05$). Priming did not affect the duration of action significantly, except in the case of PCB priming of DTC, where duration was increased from 39 ± 4.4 to 57 ± 4 min ($p < 0.02$). It is concluded that priming with a synergistic relaxant might increase speed of onset without prolonging the duration of neuromuscular blockade. However, the effect of DTC priming of PCB onset is too small to be clinically significant.

Key words

NEUROMUSCULAR RELAXANTS: pancuronium, tubocurarine; DRUG INTERACTION: pancuronium, tubocurarine; PHARMACODYNAMICS: priming principle.

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The administration of a subparalyzing dose of a non-depolarizing muscle relaxant accelerates the onset of action of a larger dose of the same drug given a few minutes later. This "priming" effect has been reported with divided doses of alcuronium,[1] atracurium,[2] pancuronium,[3] and vecuronium.[4]

Mixtures of two different non-depolarizing relaxants may produce synergism. This has been demonstrated for d-tubocurarine and pancuronium combinations in the rat phrenic nerve-hemidiaphragm preparation[5] and in humans.[6] Although the reason for this synergism is unknown, it may be the result of the action of the drugs at different sites.[6] Differences in pre- and post-synaptic activity among non-depolarizing relaxants has been suggested and the degree of train-of-four fade may be related to the relative importance of these two actions.[7] Such synergism may also be due to a post-synaptic mechanism which relies on the different affinities of relaxants for the two subunits of the receptor.[8]

This study was designed to determine the onset time, the intensity and the duration of neuromuscular blockade produced by administering a priming dose of d-tubocurarine before pancuronium or pancuronium before d-tubocurarine. The results were compared with the effect of equipotent doses of the individual agents, administered as a single bolus or in divided doses.

Methods

The study was approved by the Hospital Ethics Committee. One hundred and eight adult patients, ASA physical status I or II, were studied during various elective procedures of at least 90 min duration. Patients with hepatic, renal or neuromuscular disease were excluded, as were those with electrolyte abnormality and those taking any medication known or suspected to interfere with neuro-

TABLE I Relaxant dosage

Group	*Subparalyzing dose*	*Paralyzing dose*
I	Saline	Pancuronium 0.07 $mg \cdot kg^{-1}$
II	Pancuronium 0.007 $mg \cdot kg^{-1}$	Pancuronium 0.063 $mg \cdot kg^{-1}$
III	d-tubocurarine 0.04 $mg \cdot kg^{-1}$	Pancuronium 0.063 $mg \cdot kg^{-1}$
IV	Saline	d-tubocurarine 0.4 $mg \cdot kg^{-1}$
V	d-tubocurarine 0.04 $mg \cdot kg^{-1}$	d-tubocurarine 0.36 $mg \cdot kg^{-1}$
VI	Pancuronium 0.007 $mg \cdot kg^{-1}$	d-tubocurarine 0.36 $mg \cdot kg^{-1}$

muscular function. The patients were randomized into six groups of 18, according to the relaxant sequence to be administered (Table I).

Premedication consisted of atropine or scopolamine, 0.007–0.01 $mg \cdot kg^{-1}$, and morphine 0.1 $mg \cdot kg^{-1}$ or meperidine, 1 $mg \cdot kg^{-1}$, intramuscularly 1 h before the scheduled beginning of the surgical procedure. On arrival in the operating room, the ECG and automatic blood pressure monitors were attached. Anaesthesia was induced with thiopentone 3–5 $mg \cdot kg^{-1}$, and maintained with nitrous oxide (70 per cent) and halothane (0.5–1 per cent inspired) in oxygen.

Neuromuscular transmission was monitored according to the method of Ali *et al.*[9] The ulnar nerve was stimulated supramaximally at the elbow with square pulses of 0.2 ms in duration, delivered at a frequency of 2 Hz for 2 s by a Grass S48 stimulator. This was repeated every 12 s. The hand and forearm were immobilized in a splint and the force of contraction of the adductor pollicis muscle was measured with a Grass FT-10 force-displacement transducer and recorded on paper. A baseline was established after induction of anaesthesia, with the patient being ventilated by mask. Then, either saline, or a priming dose of either d-tubocurarine, or pancuronium, was given intravenously. Three minutes later, a paralyzing dose of relaxant was administered (Table I). The total dose given was equivalent to 0.4 $mg \cdot kg^{-1}$ d-tubocurarine or 0.07 $mg \cdot kg^{-1}$ pancuronium. Thus assuming a 6 to 1 potency ratio between pancuronium and d-tubocurarine,[10] all patients received approximately equipotent doses. The patients were intubated when maximum twitch depression was attained. Then they were ventilated using a Mapleson D circuit with a fresh gas flow of 70 $ml \cdot kg^{-1} \cdot min^{-1}$. Neuromuscular monitoring was continued until first twitch height reached ten per cent of initial control.

The speed of onset of the neuromuscular blockade was assessed by measuring the time from the injection of the paralyzing dose of relaxant until increments of ten per cent blockade of first twitch tension from 10–100 per cent. Also, the mean block at various times after administration of the paralyzing dose was calculated. The duration of block was defined as the time from injection of the paralyzing dose until spontaneous return to ten per cent twitch height.

Results are presented as mean values with standard error as an index of dispersion. Comparisons were made between (1) d-tubocurarine and pancuronium onset when given as a single dose, for which Stuent's t test was used; (2) d-tubocurarine onset with and without pretreatment and (3) pancuronium onset with and without pretreatment. Since the last two comparisons involved three groups each, the Bonferroni correction was applied.[11] Chi square analysis was applied when appropriate.

Results

The patients' sex, ages and weights are listed in Table II. All groups were comparable.

TABLE II Demographic data

Group	*Sex*	*Age (years) mean ± SEM*	*Weight (kg) mean ± SEM*
I	11 M: 7 F	49 ± 4.7	72 ± 2.8
II	7 M: 11 F	47 ± 5.1	64 ± 1.9
III	10 M: 8 F	49 ± 3.1	67 ± 2.7
I–III	28 M: 26 F	48 ± 2.5	68 ± 1.5
IV	8 M: 10 F	45 ± 4.6	66 ± 2.4
V	10 M: 8 F	46 ± 3.4	67 ± 2.5
VI	10 M: 8 F	40 ± 2.9	68 ± 2.9
IV–VI	28 M: 26 F	44 ± 2.1	67 ± 1.5
All	56 M: 52 F	46 ± 1.6	67 ± 1.0

TABLE III Maximum block and duration of action

Group	*Maximum block of first twitch (%) mean ± SEM*	*Duration (min) mean ± SEM*
I (NIL–PCB)	99.6 ± 0.2	64 ± 9.6
II (PCB–PCB)	97.2 ± 1.2	50 ± 4.5
III (DTC–PCB)	100 ± 0	64 ± 4.9
IV (NIL–DTC)	95.8 ± 1.2*	39 ± 4.4*
V (DTC–DTC)	97.6 ± 0.9	45 ± 3.0
VI (PCB–DTC)	99.8 ± 0.2†	57 ± 4.0†

*$p < 0.05$ with respect to Group I.
†$p < 0.05$ with respect to Group IV.

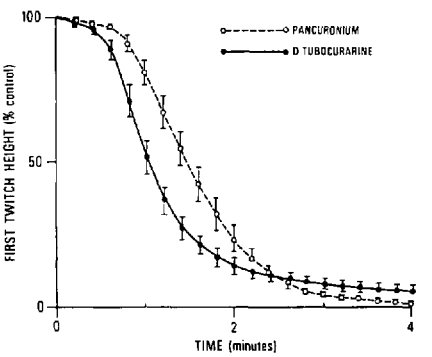

FIGURE 1 First twitch height, expressed as a percentage of control value, with respect to time after injection of a single dose of pancuronium or d-tubocurarine.

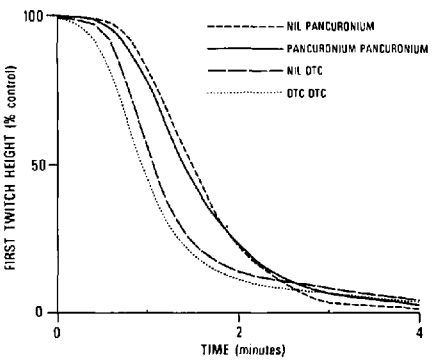

FIGURE 2 First twitch height, expressed as a percentage of control value, with respect to time after injection of a single dose or the second of divided doses of pancuronium or d-tubocurarine.

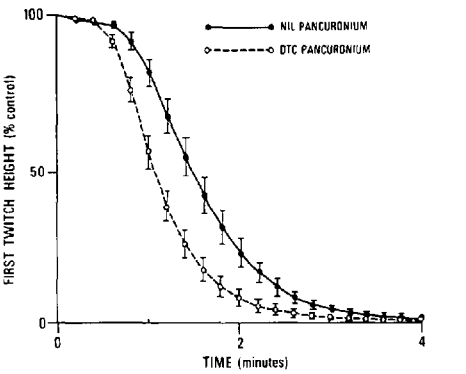

FIGURE 3 First twitch height, expressed as a percentage of control value, with respect to time after injection of pancuronium preceded by saline or by a sub-paralyzing dose of d-tubocurarine (DTC).

The maximum block attained with a single dose of pancuronium 0.07 $mg \cdot kg^{-1}$ (Group I) was slightly greater than with d-tubocurarine 0.4 $mg \cdot kg^{-1}$ (Group IV) (Table III). Three patients in Group I did not reach 100 per cent block compared with 13 patients in Group IV. This difference is statistically significant by Chi square analysis ($p < 0.005$). The onset pattern was different with the two drugs. Although the maximum block was greater with pancuronium, the onset was faster with d-tubocurarine (Figure 1). For example, mean twitch height was 51 per cent (± 6 per cent) after 1 min and 24 per cent (± 4 per cent) after 1.5 min following d-tubocurarine, compared with 81 per cent (± 4 per cent) and 48 per cent (± 6 per cent) respectively after pancuronium ($p < 0.002$ in both cases). The time to 90 per cent block was shorter with pancuronium (141 ± 11 s) than d-tubocurarine (161 ± 20 s), but this difference was not statistically significant.

Using the same relaxant for priming did not alter the maximum block significantly (Table III). Priming produced a small but insignificant acceleration of the block (approximately 10 s), especially during the first 2 min after injection (Figure 2).

Using a subparalyzing dose of d-tubocurarine before pancuronium, the onset was accelerated by about 30 s at all levels of block, when compared with pancuronium given as a single dose (Figure 3). Thus, time to 90 per cent block was 111 ± 8 versus 141 ± 11 s ($p < 0.05$). The maximum block attained was not statistically different in the two groups (Table III). When d-tubocurarine was preceded by a

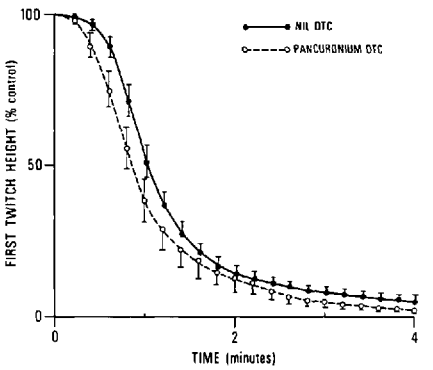

FIGURE 4 First twitch height, expressed as a percentage of control value, with respect to time after injection of d-tubocurarine (DTC) preceded by saline or by a sub-paralyzing dose of pancuronium.

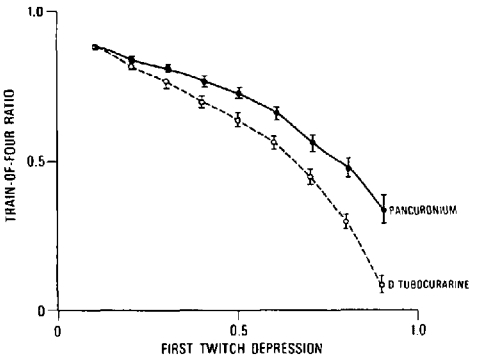

FIGURE 5 Train-of-four ratio versus first twitch depression for pancuronium and d-tubocurarine as administered as a single dose.

small dose of pancuronium, the onset time was not altered significantly when compared with a single dose of d-tubocurarine (Figure 4), but it produced a more profound block (Table III).

The duration of action was greater with a single dose of pancuronium than d-tubocurarine (Table III). Pretreatment with the same drug did not affect duration significantly. Whereas d-tubocurarine priming did not affect the duration of action of pancuronium, pancuronium priming prolonged the duration of action of d-tubocurarine (Table III).

Train-of-four fade for the same value of first twitch height depression was greater with d-tubocurarine alone than with pancuronium alone (Figure 5). Pancuronium pretreatment did not affect train-of-four fade of d-tubocurarine until intense levels of block were achieved. However, d-tubocurarine pretreatment increased fade at low levels of pancuronium blockade (Figure 6).

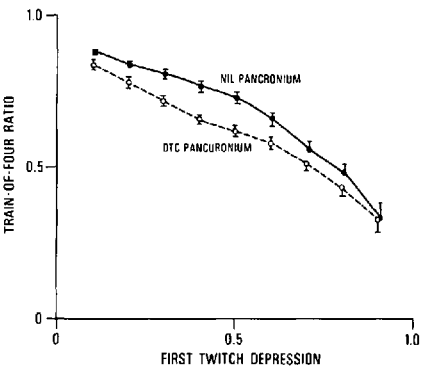

FIGURE 6 Train-of-four ratio versus first twitch depression for pancuronium preceded by saline (NIL) or d-tubocurarine (DTC).

Discussion

This study showed that giving d-tubocurarine or pancuronium in divided doses did not accelerate the onset or prolong the duration of action of either drug to a clinically significant extent. Giving d-tubocurarine before pancuronium produced a faster onset without a prolongation of the block whereas giving pancuronium before d-tubocurarine did not accelerate onset but prolonged the duration of action.

The onset patterns of d-tubocurarine and pancuronium described in this study were similar to those reported by Blackburn and Morgan.[12] The block started earlier with d-tubocurarine but this advantage seemed to be lost at more intense levels of neuromuscular blockade. However, the comparatively faster onset of pancuronium for the range 90–100 per cent block might have been due to the greater potency of 0.07 $mg \cdot kg^{-1}$ pancuronium than 0.40 $mg \cdot kg^{-1}$ d-tubocurarine (a ratio of 5.7). Pancuronium is approximately six times as potent as d-tubocurarine.[10,13] The maximum block was less with d-tubocurarine, suggesting that the doses chosen in this study were not equipotent. Many

factors may contribute to the rate of onset of neuromuscular blocking drugs, such as molecular weight, and potency.[16] The molecular weight of d-tubocurarine (682) is comparable to that of pancuronium (733) and this difference is too small to explain the faster onset of the former. At an identical degree of block, the number of molecules of relaxant bound to the acetylcholine receptors is likely to be the same for all relaxants. This amount of relaxant is carried in a smaller volume of plasma if the potency of the drug is low. Thus it is possible that the lower potency of d-tubocurarine contributes to its faster onset, because the critical number of molecules will arrive at the neuromuscular junction more rapidly.

The administration of a small priming dose of a muscle relaxant has been shown to accelerate the onset of action of the same relaxant.[1–4] No such statistically significant acceleration was demonstrated here. However, calculations based on power analysis,[15] with the standard deviations observed in this study, showed that the time to 50 per cent block would need to be shorter by at least 18 s in the pretreatment group, before an acceleration could be detected with a greater than 80 per cent probability with the number of patients in this study. However, when predicting the onset of pancuronium using a two-compartment model with biophase,[16] the calculated acceleration of onset of action with pretreatment is only 12 s. Thus, the lack of difference observed arises probably from the small difference to be detected. Such a difference, if it exists, is of little clinical significance.

However, the results of this study are markedly different from the large acceleration reported for pancuronium in a previous study.[3] Although fewer patients received pancuronium in single or divided doses in this study (36 compared with 52), it is unlikely that the differences in numbers can explain the failure to detect significant differences here. Methodological factors are probably responsible for the discrepancy. In our previous study[3] the patients who received single doses of pancuronium were given the relaxant without prior administration of saline and without the 3-min wait period. This implies that these patients received the paralyzing dose of pancuronium at an earlier time in the anaesthetic sequence, when the depressant effect of thiopentone on cardiac output was more prominent. Furthermore, the patients who were given pancuronium in divided doses were younger than those who received single doses. Cardiac output decreases with age[17] and the time to onset of neuromuscular block increases in patients with low cardiac output.[18] Therefore older patients may tend to exhibit longer onset times, and this effect might be more important than thought previously.[3]

A statistically significant acceleration of pancuronium onset was demonstrated when preceded by d-tubocurarine priming. This did not occur at the expense of prolonged neuromuscular block. In other words, the potentiation previously described for the pancuronium-d-tubocurarine combination[6] appeared as an accelerated onset when d-tubocurarine was followed by pancuronium. When pancuronium pretreatment was followed by d-tubocurarine, such an acceleration was not observed, but a deeper block and a longer duration were observed. In this case, the potentiation was seen as a deep, protracted block.

The mechanism for the potentiation between d-tubocurarine and pancuronium is uncertain, but may be related to the different sites of action of the drugs involved. Train-of-four fade is probably related to pre-synaptic activity whereas first twitch depression most likely reflects a post-synaptic effect.[7,19] In this study, d-tubocurarine exhibited more fade at the same level of twitch depression than pancuronium, thus confirming earlier work.[20,21] When d-tubocurarine was given before pancuronium, the fade observed during the onset of the block was greater than with pancuronium alone, suggesting that the presynaptic effect of d-tubocurarine contributed to the accelerate onset. Consequently, it is possible that the best combination to obtain a significant acceleration of onset would be a pretreatment dose of a predominantly pre-synaptic drug followed by a paralyzing dose of a predominantly post-synaptic agent.

Clinically, none of the relaxant schedules tested in this study produced a definite, predictable reduction in onset time. An increase in dosage may have improved onset time, but would have caused a prolonged block. Theoretically, one could improve acceleration of onset by increasing the delay between the priming and the paralyzing dose or by increasing the priming dose. A delay greater than 3 min might be unacceptable in a busy anaesthetic practice, and the administration of larger priming doses is likely to produce unpleasant symptoms in

awake patients.[22] Nevertheless, the results suggest that the shortest onset time for non-depolarizing drugs might be achieved with a judicious mixture of two relaxants which have different mechanisms of action.

References

1 *Hutton P, Morgan G, El-Hassan K, Black AMS.* Speeding the onset of neuromuscular block by alcuronium. Br J Anaesth 1983; 55: 918P.

2 *Gergis SD, Sokoll MD, Mehta M, Kemmotsu O, Rudd GD.* Intubation conditions after atracurium and suxamethonium. Br J Anaesth 1983; 55: 83S–86S.

3 *Doherty WG, Breen PJ, Donati F, Bevan DR.* Accelerated onset of pancuronium with divided doses. Can Anaesth Soc J 1985; 32: 1–4.

4 *Schwarz S, Ilias W, Lackner F, Mayrhofer O, Foldes FF.* Rapid tracheal intubation with vecuronium: the priming principle. Anesthesiology 1985; 63: 388–91.

5 *Pollard BJ, Jones RM.* Interactions between tubocurarine, pancuronium and alcuronium demonstrated in the rate phrenic nerve-hemidiaphragm preparation. Br J Anaesth 1983; 55: 1127–30.

6 *Lebowitz PW, Ramsey FM, Savarese JJ, Ali HH.* Potentiation of neuromuscular blockade produced by combinations of pancuronium and metocurine or pancuronium and d-tubocurarine. Anesth Analg 1980; 59: 604–9.

7 *Bowman WC.* Prejunctional and postjunctional cholinoceptors at the neuromuscular junction. Anesth Analg 1980; 59: 935–43.

8 *Waud BE, Waud DR.* Interaction among agents that block end-plate depolarization competitively. Anesthesiology 1985; 63: 4–15.

9 *Ali HH, Utting JE, Gray C.* Stimulus frequency in the detection of neuromuscular block in humans. Br J Anaesth 1970; 42: 967–78.

10 *Donlon JV, Ali HH, Savarese JJ.* A new approach to the study of four non-depolarizing relaxants in man. Anesth Analg 1974; 53: 934–9.

11 *Wallenstein S, Zucker LL, Fleiss JL.* Some statistical methods useful in circulation research. Circ Res 1980; 47: 1–9.

12 *Blackburn CL, Morgan M.* Comparison of speed on onset of fazadinium, pancuronium, tubocurarine and suxamethonium. Br J Anaesth 1978; 50: 361–4.

13 *Donlon JV, Savarese JJ, Ali HH, Teplik RS.* Human dose-response curves for neuromuscular blocking drugs: a comparison of two methods of construction and analysis. Anesthesiology 1980; 53: 161–6.

14 *Minsaas B, Stovner J.* Artery-to-muscle onset time for neuromuscular blocking drugs. Br J Anaesth 1980; 52: 403–7.

15 *Cohen J.* Statistical Power Analysis for the Behavioral Sciences. Academic Press, New York, 1977, pp. 17–74.

16 *Hull CJ, English MJM, Sibbald A.* Fazadinium and pancuronium: a pharmacokinetic study. Br J Anaesth 1980; 52: 1209–21.

17 *Ritschel WA.* Pharmacokinetic approach to drug dosing in the aged. J Am Ger Soc 1976; 24: 344–54.

18 *Harrison GA, Junius F.* The effect of circulation time on the neuromuscular action of suxamethonium. Anaesth Intensive Care 1972; 1: 32–40.

19 *Gibb AJ, Marshall IG.* Pre- and post-junctional effects of tubocurarine and other nicotinic antagonists during repetitive stimulation in the rat. J Physiol (London) 1984; 351: 275–97.

20 *Williams NE, Webb SN, Calvey TN.* Differential effects of myoneural blocking drugs on neuromuscular transmission. Br J Anaesth 1980; 52: 1111–5.

21 *Robbins R, Donati F, Bevan DR, Bevan JC.* Differential effects of myoneural blocking drugs on neuromuscular transmission in infants. Br J Anaesth 1984; 56: 1095–9.

22 *Rao TLK, Jacobs HK.* Pulmonary function following "pre-treatment" dose of pancuronium in volunteers. Anesth Analg 1980; 59: 659–61.

Résumé

L'effet synergistique du bromure de pancuronium (PCB) et de la d-tubocurarine (DTC) sur le début d'action du bloc neuromusculaire a été évalué chez 108 adultes classe ASA I et II anesthésiés avec du thiopentone, protoxyde d'azote et halothane. Soit du salin ou une petite dose d'amorce (priming) (de DTC 0.04 $mg \cdot kg^{-1}$ ou PCB 0.007 $mg \cdot kg^{-1}$) a été administré trois minutes avant la dose paralysante soit de DTC ou PCB. La dose totale de relaxant musculaire était l'équivalente à la DTC 0.4 $mg \cdot kg^{-1}$ ou PCB 0.07 $mg \cdot kg^{-1}$. L'activité neuromusculaire était mesurée par une stimulation utilisant l'ondée-de-quatre (train-of-four) appliquée chaque 12 secondes. Le temps pour une dépression à 50 pour cent du premier twitch était de 63 ± 4.6 s (moyenne ± SEM) avec la DTC et 88 ± 5.2 s avec le PCB ($p < 0.002$). Les temps pour un blocage à 90 pour cent n'étaient pas différents entre les deux groupes (161 ± 20 s et 141 ± 21 s respectivement). Pour un blocage neuromusculaire à la DTC, amorcé avec soit la DTC ou le PCB et pour un blocage au PCB amorcé avec du PCB a produit une accélération de moins de dix secondes à tous les niveaux de blocage. Comparativement au PCB seul, l'amorçage du bloc au PCB avec la DTC a réduit le temps de blocage à 50 pour cent de bloc à 71 ± 4.5 s ($p < 0.02$) et à 90 pour cent de bloc à 111 ± 8 s ($p < 0.05$). L'amorçage n'a pas affecté la durée d'action significativement excepté dans le cas d'amorçage au PCB pour un blocage à la DTC où la durée a augmenté de 39 ± 4.4 à 57 ± 4 min ($p < 0.02$). On conclut que l'amorçage avec un relaxant musculaire synergistique peut accélérer le début d'action sans prolonger la durée du blocage neuromusculaire. Cependant, l'effet de l'amorçage à la DTC sur le début d'action d'un blocage au PCB est minime pour être cliniquement significatif.