Potency and hourly maintenance requirement of combinations of mivacurium and pancuronium in adults

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Purpose: To evaluate the dose-response and maintenance requirements of a combination of mivacurium and pancuronium (cMP) in clinical practice.

Methods: In a randomised, open clinical study, 70 patients, 17–50 yr of age, were anaesthetised with propofol, alfentanil and nitrous oxide in oxygen. Thirty patients received mivacurium and 20 patients received pancuronium to establish dose-response curves for these agents. Hourly maintenance requirements of mivacurium and pancuronium to maintain 90–95% neuromuscular blockade (NMB) were determined. Thereafter, 20 additional patients received cMP in incremental doses to establish a cumulative dose-response curve for cMP followed by maintenance doses of cMP. NMB was recorded by adductor pollicis electromyography.

Results: The ED₉₅ values for mivacurium and pancuronium were 100 and 66 µg·kg⁻¹, respectively; and for the cMP 2:1 (in mg:mg basis), 32 µg·kg⁻¹ mivacurium together with 16 µg·kg⁻¹ pancuronium. This cMP was 1.8 times more potent than one parent agent ($P < 0.0001$). When cMP 2:1 was used, 60% of normal maintenance requirement of pancuronium reduced the requirement of mivacurium by > 90%. If cMP 20:1 was used, then 20% of normal maintenance requirement of pancuronium reduced the requirement of mivacurium by > 70%. Neostigmine 35 µg·kg⁻¹ given at T₁ 10% recovery following cMP reversed the NMB to a TOF ratio of 0.70 in 9.5 ± 3.9 min.

Conclusion: These results reflect considerable synergism between mivacurium and pancuronium. The cMP is near intermediate-acting and the NMB is easily reversed with neostigmine. By using cMP, it may be possible to save some pharmacological costs during maintenance of anaesthesia.

Objectif : Évaluer les besoins dose-réponse de même que les besoins d'entretien d'un mélange mivacurium et pancuronium (cMP) en pratique clinique.

Méthodes : Dans une étude clinique ouverte et aléatoire, 70 patients âgés de 17 à 50 ans ont été anesthésiés avec propofol, alfentanil, N₂O et O₂. Trente patients ont reçu du mivacurium et 20 patients ont reçu du pancuronium pour construire des courbes dose-réponse pour les deux médicaments. On a ensuite déterminé les besoins horaires de mivacurium et de pancuronium pour maintenir un bloc neuro-musculaire (BNM) à 90–95%. Par la suite, 20 patients supplémentaires ont reçu le cMP en doses croissantes pour établir une courbe dose-réponse cumulative pour le cMP, suivi de doses de maintien de cMP. Le bloc a été enregistré par électromyographie de l'adducteur du pouce.

Résultats : Les valeurs ED₉₅ pour le mivacurium et le pancuronium ont été respectivement de 100 et 66 µg·kg⁻¹; et pour le mélange cMP, en rapport 2:1 sur la base de mg:mg, 32 µg·kg⁻¹ pour le mivacurium et 16 µg·kg⁻¹ pour le pancuronium. Cette combinaison cMP a été 1,8 fois plus puissante que chacun des agents constituants ($P < 0.0001$). Lorsqu'on a utilisé le cMP 2:1, 60% de la dose d'entretien normale de pancuronium a réduit les besoins de mivacurium de > 90%. Si on utilisait un mélange cMP 20:1, 20% de la dose de maintien normale de pancuronium réduisait les besoins de mivacurium de > 70%. La néostigmine 35 µg·kg⁻¹ administrée lorsque le bloc produit par cMP avait récupéré à une valeur T₁ = 10% entraînait une récupération du BNM évalué par le train-de-quatre de 0,70 en 9,5 ± 3,9 min.

Conclusion : Ces résultats indiquent une synergie considérable entre le mivacurium et le pancuronium. Le mélange cMP se comporte presque comme un relaxant musculaire de durée intermédiaire dont le bloc est facilement antagonisé par la néostigmine. Par l'utilisation du cMP, il est possible de faire des économies quant aux coûts des médicaments durant le maintien de l'anesthésie.

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PANCURONIUM is a commonly used long-acting non-depolarising neuromuscular blocking agent (NMBA). It is often chosen when neuromuscular blockade (NMB) is needed for a relatively long time even though its use is frequently associated with considerable postoperative residual curarisation.^{1,2} Mivacurium is the shortest-acting NMBA currently available. Its use is not associated with residual curarisation and NMB caused by mivacurium is easily antagonised with neostigmine, or antagonism is not required.³ Unfortunately, mivacurium is expensive, especially when compared with pancuronium.

There exists a marked synergism of action when mivacurium is preceded by pancuronium, and NMB is very much prolonged.⁴ A pronounced synergism also exists between mivacurium and pancuronium when they are given simultaneously, but, surprisingly, the spontaneous recovery profile of this combination of mivacurium and pancuronium resembles that of intermediate-acting NMBAs.⁵ However, the hourly maintenance requirements of a combination of mivacurium and pancuronium have not previously been studied.

By giving mivacurium simultaneously with pancuronium, it may be possible to save some cost during maintenance of anaesthesia and still have an easily reversed NMB at the end of operation. This study was designed to evaluate the interaction between mivacurium and pancuronium by constructing dose-response curves for them and their combination (cMP), and by determining the hourly maintenance requirements and recovery profile of cMP.

Methods

After local ethics committee approval and written informed consent, we studied 70 ASA physical class I-II patients aged 17–50 yr. The patients were not taking any medication or suffering from any disease known to affect neuromuscular transmission, and all were within 30% of their ideal body weight. Premedication was comprised of 15 mg midazolam *po*. General anaesthesia was induced with 2–2.5 mg·kg⁻¹ propofol, 20 µg·kg⁻¹ alfentanil and N₂O:O₂ 2:1, and was maintained with N₂O in O₂ and continuous infusions of 5–12 mg·kg⁻¹·hr⁻¹ propofol and alfentanil up to 50 µg·kg⁻¹·hr⁻¹. The end-tidal CO₂ was kept at 38–42 mmHg.

To monitor NMB, supramaximal 2 Hz train-of-four stimuli (TOF) were given every 20 sec with a pulse width of 100 µsec (Relaxograph™, Datex, Finland). The two stimulating electrodes were positioned over the ulnar nerve, the recording electrode over the adductor pollicis muscle, the indifferent electrode on the volar surface on the base of the forefinger and the ground

electrode between the stimulating and the recording electrodes. The forearm was attached to a dorsal splint to maintain immobility. Palmar skin temperature was maintained at >33°C. When needed, the upper extremities were covered by warm blankets. The neuromuscular function monitor was calibrated following induction of anaesthesia and before administration of NMBAs. The calibration was repeated until unchanged responses were monitored for three min. All NMBAs were injected in < 5 sec into a freely running *iv* line.

The first 50 patients were randomised into two groups to receive either mivacurium or pancuronium. Group M patients (*n* = 30) received, randomly, a single bolus dose of mivacurium 50, 65 or 80 µg·kg⁻¹ (10 patients for each dose) to establish a single-dose dose-response curve for mivacurium.⁶ After the maximal response to the first dose of mivacurium, patients were given an additional bolus dose of 100 µg·kg⁻¹. Thereafter, additional bolus doses of 50 µg·kg⁻¹ mivacurium were given to determine hourly maintenance requirements of mivacurium to maintain 85–95% NMB. Group P patients (*n* = 20) received incremental doses of pancuronium to establish individual cumulative-dose dose-response curves for pancuronium, followed by maintenance doses of pancuronium of ¼ of the individual ED₉₅ every time the T₁ (first EMG response in the train-of-four series of responses) recovered to 10% of baseline. The first dose of pancuronium was 25 µg·kg⁻¹, followed by 15 µg·kg⁻¹ and a final individual dose to establish 95% NMB.⁷

The remaining 20 patients (group cMP) received incremental doses of cMP in a mg:mg ratio of 2:1 to establish individual dose-response curves for cMP. The first and the second doses of mivacurium and pancuronium were 15 and 10 µg·kg⁻¹, and 7.5 and 5 µg·kg⁻¹, respectively. Thereafter, a final individual dose of cMP was calculated to establish 95% NMB.⁷ Then, patients were randomised to receive maintenance doses of cMP in a mg:mg ratio of either 2:1 or 20:1, 10 patients for each dose, were given in order to determine the maintenance requirement of cMP to maintain a 85–95% NMB. At the end of the operation of these 20 patients, 35 µg·kg⁻¹ neostigmine together with 0.4 mg glycopyrrolate was given when T₁ had returned to 10% of the baseline. Thereafter, we measured the time to a TOF-ratio of 0.70.

A standard least squares linear regression analysis of log-doses and probit-responses was used to determine individual dose-response curves for the muscle relaxants.⁶ We used analysis of variance (ANOVA) for statistical comparisons. If the ANOVA showed significant differences between the groups, the following individual group comparisons were done by using Scheffe F-test. When analysing the maintenance requirements,

possible synergism between mivacurium and pancuronium was also evaluated by using an isobologram.⁸ Values are expressed as mean $\pm$ SD. All randomisation was done by drawing lots. A P value < 0.05 was considered statistically significant.

Results

The study groups did not differ in age or body weight (Table I). Dose-response and maintenance data for the parent agents and their combinations are presented in Table II and in Figures 1 and 2. Due to great variation of neuromuscular response, the target neuromuscular block (NMB) could be maintained in only eight patients in group M for whom the hourly maintenance requirements of mivacurium were calculated. There was little deviation from linearity in regression of log-doses and probit-responses ($r^2 = 0.9944 \pm 0.0076$). The slopes of the individual dose-response curves were slightly steeper for cMP than for the parent agents ($P < 0.05$). If one ED_{95} of a parent agent is taken as one dose-equivalent, then ED_{95} of cMP 2:1 was 0.55 ± 0.13 dose-equivalents ($P = 0.0001$ compared with the parent agents) (Table II).

When cMP was administered in a dose-ratio of 2:1, 60% of normal maintenance requirement of pancuronium reduced the requirement of mivacurium by $>90\%$

($P < 0.0001$). If cMP was administered in a dose-ratio of 20:1, then 20% of normal maintenance requirement of pancuronium reduced the requirement of mivacurium by $>70\%$ ($P < 0.0001$) (Figure 1). In group cMP, $35 \mu\text{g}\cdot\text{kg}^{-1}$ neostigmine given at T_1 10% recovery achieved a TOF ratio of 0.70 ± 3.9 min.

Discussion

We established a single dose dose-response curve for mivacurium because mivacurium is so short-acting.^{3,9} The cumulative dose technique has been shown to be valid in case of pancuronium.⁶ The ED_{95} values for

FIGURE 1 The ED_{50} (open circles) and ED_{95} (closed circles) values for mivacurium, pancuronium and their combination (cMP). The potency of the cMP is greater than if only additivity existed between mivacurium and pancuronium.

TABLE I Patient characteristics. Group M = mivacurium, group P = pancuronium and group cMP = combinations of mivacurium and pancuronium.

Group	n	Age (yr)	Weight (kg)	Height (cm)
Group M	30	36.7 ± 9.7	73.9 ± 11.6	169 ± 10
Group P	20	38.3 ± 10.4	67.9 ± 10.1	168 ± 8
Group cMP	20	35.3 ± 9.8	71.5 ± 9.1	168 ± 9
P-value	NS	NS	NS	

Values are mean $\pm$ SD.

TABLE II Dose-response and maintenance data for mivacurium ($n = 30$), pancuronium ($n = 20$) and their combination (cMP, $n = 20$). Maintenance data for cMP was determined in two dose-ratios (2:1 ($n = 10$) or 20:1 ($n = 10$) in mg:mg basis). ED_{50} and ED_{95} = doses needed to achieve 50 or 95% neuromuscular block.

	ED_{50} ($\mu\text{g}\cdot\text{kg}^{-1}$)	ED_{95} ($\mu\text{g}\cdot\text{kg}^{-1}$)	Slope (probit $\log^{-1}$)	Maintenance requirement ($\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$)	($ED_{95}\cdot\text{hr}^{-1}$)
Mivacurium	58	100	6.4	392 ± 170	3.9
Pancuronium	38 ± 7	66 ± 12	6.9 ± 1.0	33 ± 10	0.5
cMP dose-ratio 2:1			7.9 ± 1.5		
mivacurium	19 ± 4	32 ± 7		39 ± 5	1.2
pancuronium	10 ± 2	16 ± 4		19 ± 3	
cMP dose-ratio 20:1					
mivacurium				116 ± 30	
pancuronium				6 ± 2	

Values are mean $\pm$ SD.

FIGURE 2 Potentiation of effects between mivacurium and pancuronium during maintenance of neuromuscular block. The potencies of both cMPs were greater than if only additivity existed between mivacurium and pancuronium.

mivacurium and pancuronium were about the same as those previously published.³⁻⁶ The cumulative dose technique was adequate in the case of cMP because the slope of the dose-response curve for cMP was steeper than the slope of the dose-response curve for pancuronium. This indicates that insignificant amounts of mivacurium and pancuronium were metabolised during the construction of the cumulative dose dose-response curves for cMP.¹⁰

Our results support the postulated synergism between mivacurium and pancuronium and show that pancuronium has profound effects on the NMB established by mivacurium.^{4,5,11} The cMP in a dose-ratio of 2:1 (in mg:mg basis) was 1.8 times as potent as one parent agent (Figure 1). Maintenance requirements of cMP were < 50% of that of one parent agent (Figure 2). Bandom *et al.* found that a priming dose of pancuronium prolonged mivacurium-induced neuromuscular block by 100%.¹¹

The average hourly requirement of mivacurium was 392 µg·kg⁻¹·hr⁻¹. When we administered cMP in a dose-ratio of 2:1, the requirement of mivacurium was 39 µg·kg⁻¹·hr⁻¹ together with pancuronium 19 µg·kg⁻¹·hr⁻¹. This demonstrated that 60% of normal maintenance dose of pancuronium reduced the requirements of mivacurium by 90%. An interaction between mivacurium and pancuronium became even clearer when we analysed patients who received mivacurium and pancuronium in a dose-ratio of 20:1. In these patients, a small dose of pancuronium of 6 µg·kg⁻¹·hr⁻¹ reduced the requirement of mivacurium by 70% of the normal.

The hourly maintenance requirements for short-, intermediate- and long-acting NMBAs are about 5.0, 2.0 and 0.5 times their respective ED₉₅ doses.¹² In this study, these requirements for mivacurium and pancuronium were 3.9 and 0.5 times their ED₉₅ values, respectively, when administered alone. The hourly maintenance requirement of cMP was 1.2 times ED₉₅ hr⁻¹. This was between those of pancuronium and intermediate-acting NMBAs when used alone. We also found that it was easy to antagonise the NMB produced by cMP. Many investigators have documented prolonged NMB after long-acting neuromuscular relaxants despite the administration of reversal drugs.² In the cMP group, no prolonged NMB was found after reversal with neostigmine, probably because the recovery profile of cMP resembles that of intermediate-acting NMBAs.¹³⁻¹⁴

The observed synergism can be explained by our theory of α-subunit binding.⁸ Binding by a competitive antagonist (muscle relaxant) to one of the two α-subunits on the postsynaptic acetylcholine receptor is sufficient to block activation of the receptor. Accordingly, there may be a decreased interaction of a second competitive muscle relaxant with the other α-subunit if a structurally different drug already occupies one α-subunit.^{8,15} Mivacurium and pancuronium are structurally different.³⁻⁴ Consequently, more acetylcholine receptors become occupied when the cMP is used than by one parent agent and the ensuing neuromuscular block may become greater.

Clinically effective doses of pancuronium may slightly reduce the cholinesterase activity and thereby prolong the effect of mivacurium.¹⁶ However, in a dose-ratio of 20:1, a minimal dose of pancuronium decreased requirement of mivacurium by 70% which can not be explained by changes in cholinesterase activity.

The results demonstrated that cMP was a synergistic mixture and resulted in reduction of the dose required to establish NMB. More importantly, this combination had very strong supra-additive effects during maintenance of NMB. This may be a cheaper method of inducing and maintaining NMB because pancuronium is less expensive than mivacurium and reduces the requirements of mivacurium. The prices in Canada for mivacurium and pancuronium are \$0.50 and \$0.81 mg⁻¹, respectively. For example, an ED₉₅ dose of mivacurium for a 70-kg patient costs \$3.50 and hourly maintenance of NMB with mivacurium costs \$13.72. When using a cMP 2:1, these costs are on average \$2.02 and 2.44, respectively. These are only 26% of the costs of mivacurium.

In conclusion, we found that a clear synergistic effect existed between mivacurium and pancuronium

when given simultaneously. This combination was near intermediate-acting and NMB was easily reversed with neostigmine. Therefore, cMP may be a clinically useful combination of NMBAs.

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