Interactions between mivacurium and pancuronium

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Summary
We have compared the dose–response relationships of mivacurium, pancuronium and their combination, and examined the interactions by isobolographic and fractional analyses. We studied 70 adult patients during nitrous oxide–fentanyl–propofol anaesthesia. The dose–response curves were determined by probit analysis. The ED50 and ED95 values for mivacurium were 84.2 (95% confidence interval 80.2–88.1) μg kg−1 and 46.2 (40.2–52.1) μg kg−1, respectively. Corresponding values for pancuronium were 68.5 (63.7–73.2) μg kg−1 and 40.7 (35.5–45.9) μg kg−1, respectively. Isobolographic and fractional analyses of the mivacurium–pancuronium combination demonstrated a synergistic interaction. An additional 30 patients were allocated randomly to receive either mivacurium 84.2 μg kg−1 (n=15) or pancuronium 68.5 μg kg−1 (n=15). When the first twitch (T1) of TOF recovered to 25%, each patient received mivacurium 46.2 μg kg−1. The times after administration of mivacurium until T1 25% in the mivacurium–pancuronium group were 6.4 (3.5–9.4) min and 49.8 (44.7–54.9) min, respectively (P<0.0001). We conclude that the combination of mivacurium and pancuronium was synergistic and after pancuronium-induced neuromuscular block, mivacurium became a longer acting agent than the shorter agent. (Br. J. Anaesth. 1997; 79: 19–23).

Key words

Mivacurium chloride is a short-acting, non-depolarizing neuromuscular blocking agent of the benzylisoquinoline type.1,2 Pancuronium bromide is a long-acting, steroidal neuromuscular blocking agent and is often used when the estimated time of surgery is long.3 Mivacurium may be a more useful agent at the end of surgery compared with pancuronium if it retains its short-acting nature when given in combination with pancuronium. By doing this, it may be possible to maintain good clinical neuromuscular block but enable reversal in a few minutes to a safe level of recovery.

This study was undertaken to characterize the interaction of a combination of mivacurium and pancuronium in humans using the isobolographic method and to study the effects of non-depolarizing block when mivacurium was administered during recovery from pancuronium-induced neuromuscular block.

Patients and methods
After obtaining Hospital Ethics Committee approval and informed consent, we studied ASA I or II patients, aged 19–57 yr, undergoing elective surgical procedures. No patient had any disease or metabolic abnormality known to alter neuromuscular transmission, or was receiving any drug known or suspected of interfering with neuromuscular function. ECG, pulse oximetry and non-invasive arterial pressure were monitored. Palm skin temperature of the hand, where neuromuscular function was monitored, was maintained at >33°C.

INTERACTION STUDIES
Anaesthesia was induced with fentanyl 4–5 μg kg−1, propofol 2–2.5 mg kg−1 and 70% nitrous oxide in oxygen, and maintained with a continuous infusion of propofol 8–10 mg kg−1 h−1 and 70% nitrous oxide in oxygen supplemented with intermittent bolus doses of fentanyl 1–2 μg kg−1. Ventilation was adjusted to maintain normocapnia (end-tidal carbon dioxide partial pressure 4.9–5.5 kPa).

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 10 s, using a Myotest DBS peripheral nerve stimulator (Biometer Co., Odense, Denmark). The resultant contraction of the adductor pollicis was recorded using a force displacement transducer and neuromuscular function analyser (Myograph 2000, Biometer Co., Odense, Denmark). Preload tension of the thumb was maintained at 300 g throughout the investigation. The first twitch (T1) of the TOF was considered twitch height.

After stable recording of neuromuscular transmission had been established for a minimum of 30 min, we created dose–response curves for mivacurium, pancuronium and the combination of mivacurium and pancuronium in humans using the isobolographic method and to study the effects of non-depolarizing block when mivacurium was administered during recovery from pancuronium-induced neuromuscular block.
and pancuronium. For mivacurium, we used a single-dose method because mivacurium is short-acting.4 A subgroup of 30 patients was allocated randomly to receive mivacurium 30, 45 or 60 μg kg⁻¹ (10 patients for each dose). After administration of mivacurium, maximal twitch depression was assessed and anaesthesia was continued thereafter. The percentage values for twitch depression in each dose were transformed to probits and plotted against the logarithm of the dose. Subsequently, dose-response curves were obtained by least square linear regression analysis of the log-dose and probit-response values.5

Another subgroup of 20 patients received pancuronium in incremental doses to establish cumulative dose–response curves for pancuronium.6 Patients received pancuronium 30 μg kg⁻¹ as their first dose of neuromuscular blocker. Incremental doses (15 μg kg⁻¹) were administered when twitch height remained constant for three consecutive twitches. After approximately 95% depression after the last incremental dose, anaesthesia was continued as required. The percentage values for twitch depression were transformed to probit means. The cumulative dose–response curve was determined by log-probit transformation of the data. From the dose–response curves of mivacurium and pancuronium administered alone, the respective ED₉₅ and ED₅₀ (effective dose resulting in 95% and 50% reduction in T₁) values were determined.

The following predetermined doses of drugs were administered to another subgroup (20 patients): mivacurium and pancuronium, respectively, 13.9 and 12.2 μg kg⁻¹, 18.5 and 16.3 μg kg⁻¹, and 23.1 and 20.4 μg kg⁻¹. Studies of the single-drug groups were concluded first so that doses of the combination could be planned. From the dose–response curves of the neuromuscular agents administered alone, we determined the respective ED₉₅. Subsequently, dose–response curves were obtained by administration of the drug combinations in a constant dose ratio based on the ED₅₀ values of the single agent.

For the mivacurium–pancuronium combination, the following combinations after a pilot study were administered: 0.3 ED₅₀ mivacurium + 0.3 ED₅₀ pancuronium; 0.4 ED₅₀ mivacurium + 0.4 ED₅₀ pancuronium; and 0.5 ED₅₀ mivacurium + 0.5 ED₅₀ pancuronium. Regression lines were compared using analysis of covariance.

All drugs were injected over 5 s into a rapidly flowing i.v. infusion. In the combination group, drugs were injected simultaneously into two separate i.v. canulae inserted in one arm.

Isosbolographic analysis7,8 was used to define the type of interaction between mivacurium and pancuronium. This analysis has the advantage of being independent of the slopes of the dose–response curves, that is parallelism does not have to be established. It was used to confirm the interactions between neuromuscular blocking agents.9–12 If the ED₉₀ of a combination falls on the theoretical additive line, the effect of the drug mixture is additive. Points to the left of the theoretical additive line would be consistent with a synergistic interaction, whereas points to the right of the line would indicate an antagonistic interaction. Confidence intervals for each points were calculated from the variances of each component alone and were evaluated for statistical significance using the unpaired Student’s t test.

Fractional analysis13 was based on the expression of the component doses of the two agents for the combination as fractions of the doses that produce the same effect when given separately. Values near 1 indicate additive interaction, values greater than 1 imply antagonism and values less than 1 indicate synergism. This analysis was also used to confirm the interaction between neuromuscular blocking agents 10–12.

**CLINICAL STUDIES**

Selection of patients, anaesthesia and preparation for the study were similar to those described in the interaction studies. After stable recording of neuromuscular transmission for a minimum of 30 min, 30 patients were allocated randomly to receive mivacurium followed by mivacurium, or pancuronium followed by mivacurium. An ED₉₅ dose of mivacurium (84.2 μg kg⁻¹) or pancuronium (68.5 μg kg⁻¹) from the interaction studies was administered. If 90% neuromuscular block was not achieved, an additional dose (20 μg kg⁻¹) of mivacurium or pancuronium was given. Tracheal intubation was performed when neuromuscular block exceeded 95%. When the T₁ response recovered to 25% after mivacurium or pancuronium, each patient received a dose of mivacurium equivalent to the ED₅₀ (46.2 μg kg⁻¹), determined from the interaction studies. Thereafter, full spontaneous recovery of neuromuscular function was recorded in every patient. The criteria for full recovery were steady-state recovery of T₁ response and a TOF ratio > 0.7. Thereafter, anaesthesia was continued as indicated by individual patient care.

After mivacurium 46.2 μg kg⁻¹, the time from administration to maximal block was measured, and times to 1%, 25%, 75% and 95% recovery of T₁ response, and the recovery index (T₁ recovery from 25% to 75%) were recorded. The time from administration of mivacurium 46.2 μg kg⁻¹ to recovery of a TOF ratio of 0.7 was analysed.

For statistical analysis, linear regression analysis, analysis of covariance, unpaired Student’s t test and analysis of variance were used. Unless otherwise specified, the results are expressed as mean (95% confidence intervals) and were considered significant when P<0.05.

**Results**

**INTERACTION STUDIES**

Patient characteristics did not differ between groups (table 1). Calculated doses for ED₉₀ values for twitch depression were 46.2 (95% confidence interval 40.2–52.1) μg kg⁻¹ and 40.7 (35.5–45.9) μg kg⁻¹ for mivacurium and pancuronium, respectively. Corresponding ED₅₀ values were 84.2 (80.2–88.1) μg kg⁻¹ and 68.5 (63.7–73.2) μg kg⁻¹, respectively.
Interactions between mivacurium and pancuronium

The dose–response curves are shown in figure 1. The slopes for mivacurium alone, pancuronium alone, mivacurium combined with pancuronium and pancuronium combined with mivacurium were, respectively, 3.1 (2.8–3.4), 3.4 (2.9–3.9), 2.8 (2.5–3.2) and 3.0 (2.6–3.4). The slopes were not significantly different. Isobolographic analysis demonstrated synergistic interactions with respect to the neuromuscular blocking activity of the mivacurium–pancuronium combination (fig. 2).

The experimentally determined ED50 value for the combination was 8.8 (5.7–11.9) μg kg⁻¹ for mivacurium and 7.7 (5.9–9.5) μg kg⁻¹ for pancuronium. The theoretical additive ED50 value was calculated as 23.1 (17.2–29.1) μg kg⁻¹ for mivacurium and 20.4 (16.9–23.9) μg kg⁻¹ for pancuronium. The confidence intervals of these points did not overlap and the result of Student’s t test for potency ratio was significant (P<0.0001). Fractional analysis of this interaction also demonstrated synergism (table 2).

### CLINICAL STUDIES

After mivacurium 88.1 (81.3–94.9) μg kg⁻¹, there was 97 (94–99)% neuromuscular block. After pancuronium 70.8 (64.5–77.1) μg kg⁻¹, there was 96 (93–99)% neuromuscular block. The time course of mivacurium-induced neuromuscular block in the different groups are presented in figure 3. Onset times to maximum block after mivacurium 46.2 (40.2–52.1) s did not differ between the mivacurium (138.2 (109.3–167.1) s) and pancuronium (101.4 (79.2–123.6) s) groups, but there was a rapid onset time in the pancuronium group. The times after mivacurium 46.2 μg kg⁻¹ until T1 25% recovery (clinical duration) in the mivacurium and pancuronium groups were 6.4 (3.5–9.4) min and 49.8 (44.7–54.9) min, respectively (P<0.0001). Corresponding times until T1 95% recovery were 12.7 (10–15.4) min and 90.2 (83.1–97.3) min, respectively (P<0.0001). Corresponding recovery indexes were 4.7 (3.9–5.5) min and 21.8 (18.7–24.9) min, respectively (P<0.0001). Corresponding times until a TOF ratio of 0.7 were 14.2 (11.1–17.3) min and 103.4 (94.3–112.5) min, respectively (P<0.0001).

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### Table 1  Patient characteristics (mean (range or SD) or number). Mi = Pa = Combination of mivacurium and pancuronium; Mi-Mi = mivacurium followed by mivacurium; Pa-Mi = pancuronium followed by mivacurium

<table>
<thead>
<tr>
<th></th>
<th>Mivacurium</th>
<th>Pancuronium</th>
<th>Mi = Pa</th>
<th>Mi-Mi</th>
<th>Pa-Mi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>38.2 (21–54)</td>
<td>40.2 (25–55)</td>
<td>36.9 (20–53)</td>
<td>39.1 (23–57)</td>
<td>37.7 (19–56)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.7 (10.8)</td>
<td>60.9 (9.9)</td>
<td>63.7 (11.2)</td>
<td>64.8 (10.9)</td>
<td>69.2 (12.1)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.8 (11.7)</td>
<td>162.2 (10.6)</td>
<td>167.2 (11.5)</td>
<td>165.7 (12.3)</td>
<td>169.4 (12.4)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>16/14</td>
<td>8/12</td>
<td>11/9</td>
<td>8/7</td>
<td>9/6</td>
</tr>
</tbody>
</table>

### Table 2  Equipotent doses (ED50) and 95% confidence intervals for mivacurium and pancuronium administered alone and in combination in a fixed-dose ratio

<table>
<thead>
<tr>
<th></th>
<th>Mivacurium component</th>
<th>Pancuronium component</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fraction of ED50</td>
<td>Dose (μg kg⁻¹)</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>1</td>
<td>46.2 (40.2–52.1)</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Combination</td>
<td>0.19</td>
<td>8.8 (5.7–11.9)</td>
</tr>
</tbody>
</table>

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![Figure 1](image1.png) Log dose–probit plot for twitch depression for mivacurium with (■) or without (○) pancuronium, and pancuronium with (□) or without (○) mivacurium. Individual points represent mean (95% confidence intervals) twitch depression (% control) with each dose.

![Figure 2](image2.png) First twitch ED50 isobologram for the interaction of mivacurium (M) and pancuronium (P). The broken line connecting the single drug ED50 points is the theoretical additive line; the point on this line is the theoretical additive points (95% confidence intervals). The experimentally determined ED50 dose (95% confidence intervals) of the mivacurium–pancuronium (M = P) combination showed significantly synergistic effects (P<0.0001).
Discussion

Using isobolographic analysis, we have demonstrated that the combination of mivacurium and pancuronium exerted greater synergistic effect than that seen with either agent administered alone. Fractional analysis of this interaction also demonstrated a synergistic interaction, that is the effect of the combination was precisely that expected from the dose–response relationships of the individual agents. The clinical duration of action of mivacurium 46.2 μg kg\(^{-1}\) given after mivacurium was 6.4 min, while after pancuronium this mivacurium dose prolonged the clinical duration eight-fold to 49.8 min.

In this study, the calculated first twitch ED\(_{50}\) and ED\(_{95}\) values for mivacurium during nitrous oxide–fentanyl–propofol anaesthesia were 46.2 (40.2–52.1) μg kg\(^{-1}\) and 84.2 (80.2–88.1) μg kg\(^{-1}\), respectively. Similar values (52 and 81 μg kg\(^{-1}\), respectively) were reported by Savarese and colleagues\(^9\) and by Rautoma, Erkola and Meretoja\(^9\) (57.7 and 104.4 μg kg\(^{-1}\), respectively) for pancuronium calculated in this study were in close agreement (35.7 (31.9–39.8) and 64.4 (57.5–71.8) μg kg\(^{-1}\), respectively) with those reported by Gramstad and Lilleaasen,\(^{15}\) Folds and colleagues\(^{16}\) (33 and 49 μg kg\(^{-1}\), respectively) and Rautoma, Erkola and Meretoja\(^9\) (37.1 and 64.8 μg kg\(^{-1}\), respectively) during nitrous oxide–opioid–thiopentone or propofol anaesthesia. The ED\(_{50}\) and ED\(_{95}\) values of 40.7 (35.5–45.9) and 68.5 (63.7–73.2) μg kg\(^{-1}\), respectively, for pancuronium calculated in this study were in close agreement with a previous report.\(^{14}\)

Synergism between mivacurium and pancuronium may exist in children\(^{17}\) and adults,\(^{14,18}\) but we could not find any isobolographic or fractional analyses of the mivacurium–pancuronium combination. The structural similarity or dissimilarity between the interacting neuromuscular blocking agents may have an effect.\(^{19}\) Combinations of structurally similar neuromuscular blocking drugs (pipercuronium and vecuronium, rocuronium and other aminosteroids, atracurium and mivacurium) produce an additive response in isobolographic analyses.\(^{9,11}\) Structurally different blockers may potentiate each other more than structurally similar blockers.\(^{14,19,20}\)

Rautoma, Erkola and Meretoja\(^{14}\) reported that the combined use of mivacurium and pancuronium could reduce their requirements by approximately 40%. In this study, the sum of fractions for the mivacurium–pancuronium combination was 0.38 compared with the ED\(_{50}\) value of mivacurium or pancuronium (table 2). This combination could reduce requirements by 62%. The methodological difference between the study of Rautoma, Erkola and Meretoja and the present investigation is only a combination of 0.5 times the ED\(_{50}\) of mivacurium and pancuronium. But we obtained the ED\(_{50}\) for the combination of drugs from the dose–response curves (fig. 1) analysed by isobolographic and fractional analyses (fig. 2, table 2). In another study where atracurium and vecuronium were used together, the maximal reduction in drug consumption was approximately 30%.\(^{21}\)

Synergism between mivacurium and pancuronium (which have dissimilar molecular structures) may be related to their differential actions on pre- and postsynaptic acetylcholine receptors,\(^{19}\) differential sensitivity of the α-subunit acetylcholine recognition sites\(^{22}\) and effects on plasma cholinesterase.\(^{23}\)

In a study in which mivacurium 70 μg kg\(^{-1}\) was given at T1 25% during recovery from pancuronium block, the clinical duration was prolonged from 10 to 54 min compared with that after mivacurium block alone.\(^{18}\) In this study, we also obtained similar changes in clinical duration (from 6.4 (3.5–9.4) min to 49.8 (44.7–54.9) min) for a mivacurium dose of 46.2 μg kg\(^{-1}\). It has been suggested that the long elimination half-life of the underlying longer acting blocker prolongs the effects of the subsequent shorter acting drug.\(^{24}\)

The clinical duration of action after pancuronium 80 μg kg\(^{-1}\) was 44 (SD 10) min during nitrous oxide–opioid–thiopentone anaesthesia.\(^{25}\) In this study, a similar clinical duration (49.8 (44.7–54.9) min) was obtained after mivacurium in the pancuronium group. It was suggested that after pancuronium-induced neuromuscular block, mivacurium became a longer acting agent than the shorter agent, but shorter than the longer agent. Middleton and colleagues\(^{26}\) suggested that the majority of receptors remain occupied by the drug administered initially; clinical duration depends more on the kinetics of the first neuromuscular blocking drug than the subsequently administered drug.

Pancuronium is known to inhibit plasma cholinesterase which degrades mivacurium.\(^{2,23,27}\) Plasma cholinesterase activity has been shown to decrease by 15% or less after pancuronium 20 μg kg\(^{-1}\).\(^{23}\) On the other hand, clinically useful doses of pancuronium have been noted to inhibit plasma cholinesterase in vitro to a clinically insignificant amount.\(^{28}\) A small dose of mivacurium might have
only minimal effects on plasma cholinesterase. Therefore, we did not investigate effects on plasma cholinesterase.

We conclude that the interaction of mivacurium and pancuronium was the result of synergistic actions at the neuromuscular junction, and after pancuronium-induced neuromuscular block, mivacurium became a longer acting agent than the shorter agent.

References