Dose–response studies of the interaction between mivacurium and suxamethonium

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Summary
We have determined the effect of pretreatment with mivacurium on the potency of suxamethonium and the effect of prior administration of suxamethonium on the potency of mivacurium. We studied 100 ASA I or II patients during thiopentone–fentanyl–nitrous oxide–isoflurane anaesthesia. Neuromuscular block was recorded as the evoked thenar mechanomyographic response to train-of-four stimulation of the ulnar nerve (2 Hz at 12-s intervals). Single dose–response curves were determined by probit analysis. Pretreatment with mivacurium had a marked antagonistic effect on the development of subsequent depolarizing block produced by suxamethonium. The dose–response curves for suxamethonium alone and after pretreatment with mivacurium did not deviate from parallelism, but those constructed after mivacurium were shifted significantly to the right (P < 0.0001). The calculated doses producing 50% depression of T1 (ED50) were 86 (95% confidence intervals 83–88) and 217 (208–225) μg kg⁻¹ for suxamethonium alone and after mivacurium, respectively. This study also demonstrated that prior administration of suxamethonium did not appear to influence either the slope of the regression lines or the potency of mivacurium. Combining the results of this study with a previous study (mivacurium ED50 = 20.8 (20.3–21.3) μg kg⁻¹ during isoflurane–nitrous oxide anaesthesia), we suggest that the potency of mivacurium did not differ from that observed after suxamethonium (17.4 (16.9–17.9) μg kg⁻¹). (Br. J. Anaesth. 1995; 74: 26–30)

Key words

Mivacurium chloride is a short-acting, non-depolarizing neuromuscular blocking agent that has recently been introduced into clinical practice [1, 2]. It is hydrolysed by plasma cholinesterase at a rate 70% of that of suxamethonium [3]. The effects of the interaction between suxamethonium and non-depolarizing neuromuscular blocking agents depend upon the order of administration and doses used [4–16]. Previous studies of the effects of suxamethonium on the neuromuscular effects of subsequently administered non-depolarizing neuromuscular blocking drugs in patients have produced conflicting results. Several investigators reported potentiation of the effects of tubocurarine [4], pancuronium [5], vecuronium and atracurium [6–8] by prior administration of suxamethonium. In contrast, Walts and Dillon [9] noted the opposite for tubocurarine. Others found no significant influence for suxamethonium on the subsequent administration of pancuronium, doxacurium, pipercuronium or rocuronium [10–13]. On the other hand, prior administration of small doses of different non-depolarizing neuromuscular blocking drugs had an antagonistic effect on the development of subsequent depolarizing block produced by suxamethonium [14–16].

The detailed interactions of mivacurium and suxamethonium have not been studied previously. Therefore, the purpose of this study was twofold: (a) to compare dose–response data for suxamethonium alone and after pretreatment with mivacurium 21 μg kg⁻¹ and (b) to compare the dose–response curves for mivacurium alone and after complete recovery from a preceding bolus administration of suxamethonium 1 mg kg⁻¹.

Patients and methods
After obtaining institutional approval and informed consent, we studied 100 ASA I or II patients of both sexes, aged 16–55 (mean 31.9) yr and weight 45–88 (mean 65.6 (SD 11.5)) kg. All patients were undergoing elective procedures, had no neuromuscular, hepatic or renal disease, and were not receiving any drug known or suspected to interfere with neuromuscular function. All patients were premedicated with lorazepam 2 mg orally approximately 90 min before induction of anaesthesia. An i.v. infusion of lactated Ringer’s solution was commenced before induction of anaesthesia. ECG, pulse oximetry and arterial pressure were monitored. Temperature was maintained at 36.5 ± 0.5 °C.

Anaesthesia was induced with thiopentone 5 mg kg⁻¹ and maintained with 60% nitrous oxide in oxygen supplemented with fentanyl 2 μg kg⁻¹ and
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isoflurane via a face mask. The trachea was sprayed with 4 ml of 4% lignocaine and intubated without the use of neuromuscular blockers. After intubation, the end-tidal concentration of isoflurane was adjusted to 1.2% (1 MAC excluding nitrous oxide). The concentrations of isoflurane, nitrous oxide, oxygen and carbon dioxide were determined continuously by a multiple-gas analyser (Capnomac, Datex Instrumentation Corporation, Helsinki, Finland). Ventilation was adjusted to maintain normocapnia (end-tidal carbon dioxide partial pressure 4.8–5.3 kPa).

While end-tidal concentrations were stabilized for 30 min, monitoring of neuromuscular block started only 10 min before administration of the neuromuscular blocker. The ulnar nerve was stimulated supramaximally at the wrist with square pulses of 0.2-ms duration, delivered in a train-of-four (TOF) sequence at 2 Hz every 12 s, using a Myotest peripheral nerve stimulator (Biometer International, Odense, Denmark). The resultant contraction of the adductor pollicis muscle was recorded using a force displacement transducer and neuromuscular function analyser (Myograph 2000, Biometer International, Odense, Denmark). Preload tension of the thumb was maintained at 300 g throughout the investigation.

Patients were allocated randomly to three groups. In group I, suxamethonium 50, 100 or 200 μg kg⁻¹ was administered in a random order to three subgroups of 10 patients each. Patients in group II received mivacurium 21 μg kg⁻¹ (1 × ED₉₀ during thiopentone–fentanyl–nitrous oxide–isoflurane anaesthesia [17]) as pretreatment. In group II, after maximum twitch depression of the pretreatment was identified, suxamethonium 100, 200, 300 or 450 μg kg⁻¹ was administered in a random fashion to four subgroups of 10 patients each. Patients in group III received suxamethonium 1 mg kg⁻¹, and after complete recovery from depolarizing block, mivacurium 10, 25 or 40 μg kg⁻¹ was administered in a random fashion to three subgroups of 10 patients each. In the latter group, the dose–response data were compared with the data previously obtained by Naguib and co-workers under identical experimental conditions, but in the absence of prior suxamethonium [17]. All drugs were given over 5 s into a rapidly flowing i.v. infusion. The neuromuscular response was recorded as maximum depression of T₁, expressed as a percentage of the control value. When the maximum effect of the selected dose was reached, the study was terminated and anaesthesia continued as appropriate for surgery. Onset of neuromuscular block was the interval between administration of suxamethonium in groups I and II, or mivacurium in group III, until maximum depression of twitch height.

Depression of T₁ (expressed as a percentage of the control value) in each group was transformed to logits and plotted against the logarithm of the dose using PCNONLIN version 4.2A (ClinTrials, Inc., Lexington, KY, USA) [18]. Regression lines were compared using analysis of covariance. First, we tested the lines to determine if they deviated from parallelism. If they did not, an F test was applied to determine if the elevations were different. If so, a t test was applied to determine which line differed from parallelism. If the data were compared using analysis of variance, we compared age and body weight between the different groups. Unpaired Student’s t tests were used where appropriate. Results are expressed as mean (95% confidence intervals) and were considered significant when P < 0.05.

Results

POTENCY ESTIMATES OF SUXAMETHONIUM

The mean T₁ and TOF ratio observed after pretreatment with mivacurium 21 μg kg⁻¹ (group II) were 71 (95% confidence intervals 62–81)% of

![Figure 1](https://academic.oup.com/bja/article-abstract/74/1/26/260900/15117260900) Myographic recordings obtained after administration of suxamethonium (S) 200 μg kg⁻¹ alone in a patient in group I (A) and suxamethonium 200 μg kg⁻¹ after pretreatment with mivacurium 21 μg kg⁻¹ in a patient in group II (B). A: Maximum block occurred after 25 s and T₁ at maximum block was 20% (of control tension). Recovery from maximum depression to control twitch height occurred 197 s after administration of suxamethonium. B: T₁ height was 82% of control before administration of suxamethonium. After administration of suxamethonium 200 μg kg⁻¹, maximum block was observed after 42 s, at which time T₁ was 25% (of control tension). Recovery to pre-suxamethonium T₁ height (82% of control) occurred 286 s after administration of suxamethonium (not shown). The fade observed in the TOF stimulation in recording A was because of the use of isoflurane in this study.
Table 1  Mean (95 % confidence intervals) doses of suxamethonium (with and without mivacurium pretreatment) required for 50 % (ED₅₀) and 80 % (ED₈₀) depression of T₁. ***P < 0.0001 compared with the corresponding value in patients who received mivacurium pretreatment.

<table>
<thead>
<tr>
<th></th>
<th>ED₅₀ (µg kg⁻¹)</th>
<th>ED₈₀ (µg kg⁻¹)</th>
<th>Slope of probit response vs logarithm of dose</th>
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<tbody>
<tr>
<td>Without mivacurium</td>
<td>86 (83–88)***</td>
<td>135 (130–141)***</td>
<td>4.2 (3.9–4.4)</td>
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<td>pretreatment</td>
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<tr>
<td>After mivacurium</td>
<td>217 (208–225)</td>
<td>420 (389–450)</td>
<td>2.9 (2.6–3.2)</td>
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<td>pretreatment</td>
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control tension and 0.68 (0.57–0.77), respectively. These effects were observed after 366 (331–401) s. A representative result of the effects of suxamethonium administered alone and after mivacurium pretreatment is shown in figure 1.

The ED₅₀ and ED₈₀ values for suxamethonium alone and after mivacurium are presented in table 1. Pretreatment with mivacurium significantly (P < 0.0001) increased all ED values for suxamethonium (table 1). Some of the calculated ED values were not reported because they were outside the range of doses tested. The slope of the line describing T₁ depression after suxamethonium in group I was not significantly different from the corresponding line in group II who received mivacurium pretreatment (table 1, fig. 2). The lines constructed for group II were shifted significantly to the right (P < 0.0001).

Table 2  Mean (95 % confidence intervals) doses of mivacurium (with and without prior suxamethonium) required for 50 % (ED₅₀), 80 % (ED₈₀) and 95 % (ED₉₅) depression of T₁

<table>
<thead>
<tr>
<th></th>
<th>ED₅₀ (µg kg⁻¹)</th>
<th>ED₈₀ (µg kg⁻¹)</th>
<th>ED₉₅ (µg kg⁻¹)</th>
<th>Slope of probit response vs logarithm of dose</th>
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<tr>
<td>Without prior suxamethonium [17]</td>
<td>20.8 (20.3–21.3)</td>
<td>28 (27–29)</td>
<td>37.4 (35.8–39)</td>
<td>5.0 (4.6–5.4)</td>
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<tr>
<td>After suxamethonium</td>
<td>17.4 (16.9–17.9)</td>
<td>27 (26–28)</td>
<td>38 (36–40)</td>
<td>4.4 (4.05–4.7)</td>
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Figure 2  Log dose–probit plot for T₁ depression after administration of suxamethonium alone (●) or after mivacurium pretreatment (■). Individual points represent the mean value attained with each dose and bars represent 95 % confidence intervals.

Figure 3  Log dose–probit plot for T₁ depression after administration of mivacurium with (●) and without (■) prior suxamethonium. The curve for the group without suxamethonium is taken from Naguib and colleagues [17]. Individual points represent the mean value attained with each dose and bars represent 95 % confidence intervals.
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Administration of suxamethonium 1 mg kg⁻¹ to group III resulted in 100% neuromuscular block in all patients. Twitch response ceased after 36 (32-40) s and returned to 100% of control tension after 707 (649-764) s. The dose-response curve after administration of different doses of mivacurium after prior suxamethonium is shown in figure 3. The calculated T1 ED₅₀, ED₉₀ and ED₉₅ values were given in table 2. Table 2 also shows, for comparison, data obtained previously without prior administration of suxamethonium [17]. The regression lines did not deviate from parallelism and the calculated ED₅₀, ED₉₀ and ED₉₅ values did not differ significantly between groups.

We did not observe any substantial haemodynamic changes during the 30-min period of stabilization of end-tidal anaesthetic concentrations.

Discussion

The results of this study demonstrated that prior administration of mivacurium had a marked antagonistic effect on the development of subsequent depolarizing block produced by suxamethonium, and the regression lines for suxamethonium block with and without mivacurium pretreatment were parallel (fig. 2, table 1). The calculated ED₅₀ and ED₉₀ values were more than doubled after mivacurium pretreatment (table 1). We interpret these findings collectively as indicative of competitive antagonism between the two drugs at the post-junctional receptors. We waited for the maximum effect of mivacurium pretreatment to occur before administration of suxamethonium. This was observed after 366 (331–401) s. As a result of the marked antagonistic effect of mivacurium, only the ED₅₀ and ED₉₀ values were within the range of doses tested. Similar observations were noted by Szalados, Donati and Bevan after administration of tubocurarine 50 μg kg⁻¹, 3 min before suxamethonium [20]. They noted that the potency of suxamethonium was decreased by approximately 50% in patients who were pretreated with tubocurarine and the calculated ED₉₀ and ED₉₅ values after tubocurarine pretreatment were outside the range of doses tested. In clinical practice, however, a dose of mivacurium as high as that used in this study would not normally be used for pretreatment, so this effect of antagonism of suxamethonium may not be as intense with smaller doses of mivacurium.

Our estimates obtained in this study for suxamethonium T1 ED₅₀ (86 μg kg⁻¹) was similar to that reported by Miller and colleagues [21], who were using a different methodology, during 1.25 MAC of isoflurane anaesthesia and single twitch stimuli. Their ED₉₀ value was 3.4 mg m⁻². This corresponds to 88 μg kg⁻¹, assuming a surface area of 1.81 m² and weight 70 kg. Caldwell and colleagues reported a higher T1 ED₅₀ value (123 μg kg⁻¹) during 1.25 MAC of isoflurane anaesthesia [22]. This difference in results could be attributed to the difference in techniques used for generating the dose-response data. In the current study we used the single-dose technique, but both Miller and colleagues [21] and Caldwell and co-workers [22] used the cumulative dose technique. They administered three [21] to five [22] different doses of suxamethonium, respectively, to each patient during the same anaesthetic after allowing for suitable recovery from the effects of the previous dose. With such a technique, each dose of suxamethonium probably has influenced the response to subsequent doses. In fact, Smith, Donati and Bevan noted that the cumulative dose technique underestimated the potency of suxamethonium [23].

The effect of prior administration of suxamethonium on a subsequent block induced by non-depolarizing blocking drugs has produced conflicting results. In the current study, we were not able to find any significant difference in the potency of mivacurium administered after recovery from suxamethonium block compared with a previous study using the same methodology, with the exception of prior administration of suxamethonium [17]. The calculated ED₅₀, ED₉₀ and ED₉₅ values were similar whether mivacurium was administered alone or preceded by suxamethonium (table 2, fig. 3), indicating no potentiation of the effect of mivacurium by prior administration of suxamethonium. The lack of an effect of suxamethonium on subsequent mivacurium-induced neuromuscular block, however, depends on our retrospective control data [17]. Maddineni, Mirakhur and McCoy [24] reported that prior administration of suxamethonium had no significant effect on the actions of mivacurium with respect to recovery indices and time to recovery of TOF to 0.70.

In conclusion, this study demonstrated that during thiopentone-fentanyl-nitrous oxide-isoflurane anaesthesia, prior administration of mivacurium had a marked antagonistic effect on the development of subsequent depolarizing block produced by suxamethonium. In addition, we found that prior administration of suxamethonium did not affect the potency of mivacurium.

References

7. Omo K, Manabe N, Ohta Y, Morita K, Kosaka F. Influence


24. Maddineni VR, Mirakhur RK, McCoy EP. Intubating conditions and neuromuscular effects after mivacurium with or without prior suxamethonium. British Journal of Anaesthesia 1993; 71: 312P.