COMPARISON OF MIVACURIUM AND SUXAMETHONIUM ADMINISTERED BY BOLUS AND INFUSION


Mivacurium chloride (BW B1090U), a new short-acting non-depolarizing neuromuscular blocking drug, has undergone initial clinical trials to evaluate its neuromuscular and cardiovascular effects [1-7]. Mivacurium is metabolized by pseudocholinesterase at a rate 70% of that of suxamethonium [8]. Because of its relatively short duration of action, mivacurium may be useful as a bolus to facilitate tracheal intubation and as an infusion to maintain extended neuromuscular block. This study of healthy adult patients undergoing surgery was designed to compare the onset of neuromuscular block and the ease of tracheal intubation after near equipotent bolus doses of mivacurium or suxamethonium, to define the infusion requirements and recovery pattern following cessation of mivacurium or suxamethonium infusion, and to test the predictive value of the time to recovery of 5% neuromuscular transmission (T5) after an initial bolus in determining the infusion requirements for mivacurium or suxamethonium.

PATIENTS AND METHODS

We studied 30 healthy adults (ASA physical status I or II) aged 18-57 yr. All patients underwent low to moderate risk elective surgical procedures requiring tracheal intubation. Women of childbearing age were excluded. No patient received aminoglycoside antibiotics or antihistamine drugs within 48 h of the study, which was approved by the Institutional Review Board of Presbyterian Hospital. Informed consent was obtained from each participant.

Patients received diazepam 0.1-0.2 mg kg⁻¹ by
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mouth) or morphine 0.05–0.10 mg kg$^{-1}$ i.m. with hyoscine or atropine 1 h before anaesthesia was induced. Venous blood samples were obtained before operation for measurement of plasma cholinesterase activity and dibucaine number. Anaesthesia was induced with thiopentone 3–10 mg kg$^{-1}$ and fentanyl 1–6 μg kg$^{-1}$ i.v. and maintained with 70% nitrous oxide in oxygen; additional thiopentone or fentanyl was given as needed.

After induction of general anaesthesia the ulnar nerve was stimulated supramaximally with repeated trains-of-four (TOF) (2 Hz for 2 s at 20-s intervals) via surface electrodes at the wrist. The evoked compound electromyogram of the adductor pollicis muscle was recorded using a Datex monitor. The arm was positioned on an armboard and protected from movement by surgical drapes. Temperature of the hand was not measured. A single bolus of either suxamethonium 1 mg kg$^{-1}$ or mivacurium 0.25 mg kg$^{-1}$ was administered over 5 s through a T-connector into a rapidly flowing i.v. infusion. Patients were allocated randomly to receive either mivacurium or suxamethonium.

The percent neuromuscular block resulting from the bolus and infusion of drug was calculated from the amplitude of the first of the TOF responses (T1) at that time compared with the T1 response before drug administration. After the infusion was stopped, recovery was determined from the amplitude of the maximum, stable T1 response at the end of the study; at this time the TOF ratio (T4:T1) was greater than 0.9.

Tracheal intubation was attempted 1 min after the bolus of suxamethonium or 1.5 min after the bolus of mivacurium if at least 80% neuromuscular block had been achieved. If the block was less than 80%, the attempt was delayed until \( \geq 80\% \) block was established. Because of the study design, any cardiovascular effects of the blocking agent per se could not be distinguished from those related to laryngoscopy and intubation and are, therefore, not reported. Conditions for intubation were scored as: excellent (no resistance to laryngoscopy, no movement of the vocal cords, no movement of the diaphragm, and no coughing after intubation); good (no resistance to laryngoscopy, no movement of the vocal cords, but slight coughing or movement of the diaphragm after intubation); fair (no resistance to laryngoscopy, but movement of the vocal cords and coughing after intubation); poor (intubation could not be accomplished because of patient movement or coughing).

When neuromuscular transmission returned to approximately \( T_S \) after the initial dose of blocking drug, a continuous infusion of mivacurium or suxamethonium was started. The infusion was continued for as long as surgical relaxation was needed. The infusion rate was adjusted to maintain neuromuscular block between 89 and 99%. Mivacurium 0.2 mg ml$^{-1}$ or suxamethonium 2.0 mg ml$^{-1}$ was delivered from a 250-ml macro-drop infusion burette (Abbott). (Solutions of mivacurium 0.5 mg ml$^{-1}$ in 5% Dextrose are stable at room temperature for at least 48 h.) The volume of myoneural blocker infused was noted every 3 min. The infusion rate (IR) (μg kg$^{-1}$ min$^{-1}$) needed to maintain block at 89–99% was then calculated. The number of 3-min epochs during which neuromuscular block was outside this range was recorded.

After the infusion was stopped, spontaneous recovery of neuromuscular transmission was observed for as long as possible. The times between cessation of infusion and recovery to 5% \( (T_5) \), 25% \( (T_{25}) \), 50% \( (T_{50}) \), 75% \( (T_{75}) \), and 95% \( (T_{95}) \) of baseline were noted where available. The 5–95% \( (T_5-T_{95}) \) and 25–75% \( (T_{25}-T_{75}) \) recovery indices were calculated. If clinically indicated, residual neuromuscular block from mivacurium was antagonized with neostigmine and atropine or glycopyrrolate.

Standard errors are shown for all mean values. Data were analysed where appropriate by linear regression, two-tailed Student’s \( t \) test, Mann–Whitney test, or chi-square analysis. The correlation between time from injection of the bolus of either suxamethonium or mivacurium to recovery of neuromuscular transmission to \( T_S \) and the steady-state infusion rate was tested by a linear least-squares regression analysis. Differences were considered statistically significant at \( P < 0.05 \).

RESULTS

Bolus doses of mivacurium and suxamethonium

Sixteen patients were given suxamethonium and all developed complete neuromuscular block after the initial bolus dose. Twelve of the 14 patients who received mivacurium 0.25 mg kg$^{-1}$ developed complete block after the initial bolus dose. Two of the patients given mivacurium had less than 50% block 90 s after the initial bolus and
were given a supplementary bolus dose (0.02 and 0.10 mg kg\(^{-1}\)). Because the second dose of mivacurium was given before maximal block developed, these patients were excluded from analysis of onset time, intubation efficacy and correlation between \(T_s\) and infusion rate. The mean (SEM) time from administration of the initial bolus dose to maximum neuromuscular block (onset time) was 2.5 (0.3) min for patients given mivacurium and 1.0 (0.1) min for patients given suxamethonium (table I). The mean time from administration of the initial dose of blocking drug to recovery to \(T_s\) was 17.5 (1.8) min after mivacurium and 6.4 (0.7) min after suxamethonium.

The time from administration of the neuromuscular blocker to tracheal intubation was less for suxamethonium than for mivacurium. Four of the 12 patients given a single dose of mivacurium met the criterion for neuromuscular block and underwent successful intubation 1.5 min after the dose. In eight of 12 patients \(< 80\%\) blockade was present after 1.5 min and intubation was delayed. In one of these patients intubation was attempted 1.7 min after the mivacurium dose and was unsuccessful because of factors other than the depth of anaesthesia and the degree of block. This patient was therefore excluded from analysis of intubation conditions. The mean time from administration of mivacurium to successful intubation was 2.0 (0.2) min (range 1.5–3.3 min; \(n = 12\)).

Thirteen patients given suxamethonium met the criterion for neuromuscular block and intubation was performed at 1 min or earlier; one patient underwent intubation 45 s after suxamethonium. Three patients given suxamethonium underwent intubation later than the prescribed time. In one patient, \(< 80\%\) block was present 1.3 min after the suxamethonium dose, but intubation was performed 1.5 min after the bolus dose, when \(96\%\) block was present. In another patient, the mouth could not be opened until 80 s after the bolus dose, despite the presence of complete block at 60 s. This patient’s trachea was intubated successfully 80 s after the suxamethonium. He exhibited no increase in heart rate or temperature and the anaesthetic continued without incident. In the third patient, other aspects of his care delayed tracheal intubation despite the presence of \(80\%\) block 1 min after the suxamethonium. The mean time from administration of suxamethonium to successful intubation was 1.1 (0.1) min (range 0.75–2 min; \(n = 16\)). Intubation conditions were rated as excellent or good in all patients (mivacurium: excellent = 9, good = 2; suxamethonium: excellent = 12, good = 4).

One patient had transient facial flushing after the bolus dose of suxamethonium. Ten of the 14 patients given mivacurium had facial or truncal flushing, or both, after the bolus dose. Flushing in both the suxamethonium and the mivacurium-
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Table III. Relationship of $T_5$ and infusion rate (mean (SEM) range). $T_5$ is time from injection to recovery of twitch response to $5^{th}$ of baseline transmission. Linear regression equations: mivacurium, $IR = 13 - 0.4 \times T_5$; suxamethonium, $IR = 189 - 14 \times T_5$

<table>
<thead>
<tr>
<th>Drug</th>
<th>$T_5$ after bolus (min)</th>
<th>Infusion rate ($\mu g , kg^{-1} , min^{-1}$)</th>
<th>$r$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mivacurium</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>$(n = 11)$</td>
<td>17.5 (1.8)</td>
<td>6.7 (1.0)</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>[11-32.3]</td>
<td>[3.6-13.5]</td>
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<tr>
<td>Suxamethonium</td>
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<tr>
<td>$(n = 11)$</td>
<td>6.4 (0.7)</td>
<td>98.7 (12.6)</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>[3.3-11.6]</td>
<td>[56-165]</td>
<td></td>
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</tbody>
</table>
tive correlation between recovery to $T_5$ and infusion rate for both agents (table III).

**DISCUSSION**

The ED$_{95}$ for mivacurium in adults [1] is 58 $\mu$g kg$^{-1}$; mivacurium 250 $\mu$g kg$^{-1}$ was used in this study—approximately four times the ED$_{95}$. Suxamethonium 1 mg kg$^{-1}$ was estimated as an equipotent dose of four times the ED$_{95}$ [9]. The time from injection to maximum block (onset time) was significantly shorter after suxamethonium than after mivacurium. This may reflect fundamental differences in the mechanism of action between non-depolarizing and depolarizing neuromuscular blocking agents [10].

With large doses of thiopentone supplemented by opioids or topical or i.v. lignocaine, or both, the trachea can be intubated without blockade in many patients. However, we decided not to attempt intubation unless at least 80% neuromuscular block was present. Intubating conditions at maximum neuromuscular block were comparable with both agents. Most patients given mivacurium had facial or truncal flushing, or both, which we presume was a peripheral manifestation of histamine release [11,12].

After a bolus of suxamethonium, neuromuscular transmission recovered to 5% approximately 10 min earlier than after mivacurium. There was no relation between the time to recovery to $T_5$ and plasma cholinesterase activity or dibucaine number in the mivacurium or suxamethonium-treated patients in this study. Intubating conditions at maximum neuromuscular block were comparable with both agents. Most patients given mivacurium had facial or truncal flushing, or both, which we presume was a peripheral manifestation of histamine release [11,12].

Mivacurium has a longer onset time than suxamethonium and may be associated with a greater incidence of histamine release after rapid bolus administration. The duration of action and rate of spontaneous recovery appear to be markedly shorter for mivacurium than for any currently available non-depolarizing neuromuscular blocking agent. Maintenance of continuous blockade by infusion is accomplished as easily with mivacurium as with suxamethonium and is not accompanied by the phase II block associated with suxamethonium. Individual infusion requirements can be estimated from the time to $T_5$ recovery after an initial bolus.

**ACKNOWLEDGEMENT**

This study was supported in part by a grant from Burroughs Wellcome Co.

**REFERENCES**

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