Onset/offset characteristics and intubating conditions of rapacuronium: a comparison with rocuronium


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We compared onset and offset of action and tracheal intubating conditions after rapacuronium and rocuronium in 60 patients in a randomized, assessor-blinded study. Following induction of anaesthesia with propofol 2.5 mg kg\(^{-1}\), either rapacuronium 1.5 mg kg\(^{-1}\) (n=30) or rocuronium 0.6 mg kg\(^{-1}\) (n=30) was administered to facilitate tracheal intubation. Anaesthesia was maintained with either a propofol infusion (100 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)) or sevoflurane (1% end-tidal) with 66\% nitrous oxide (N\(_2\)O), n=15 in each subgroup. Neuromuscular monitoring was performed using an electromyographic (EMG) device (Datex Relaxograph). The lag times (mean 42 (SD 11) s and 44 (16) s), maximum block (99 (2)% and 98 (3)%), and intubating conditions at 60 s (good-to-excellent in 86\% and 84\% of patients) were similar for rapacuronium and rocuronium, respectively. The onset time of rapacuronium was shorter than rocuronium (87 (20) vs 141 (65) s, P<0.001), and the degree of block at 60 s was greater (69 (26) vs 50 (27)%). Twenty-five per cent recovery was shorter with rapacuronium than rocuronium during propofol (15.0 (3.2) vs 39.1 (14.2) min, P<0.001) and sevoflurane (15.1 (4.2) vs 47.8 (19.0) min, P<0.001) anaesthesia. We conclude that rapacuronium 1.5 mg kg\(^{-1}\) had a more rapid onset, similar intubating conditions, and shorter recovery times than rocuronium 0.6 mg kg\(^{-1}\).

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Rapacuronium (ORG 9487), the 16-N-allyl, 17-β-propionate analogue of vecuronium, is a new aminosteroidal non-depolarizing neuromuscular blocking agent with a rapid onset and short duration of action.\(^1\)\(^-\)\(^4\) It is less potent than rocuronium, requiring a minimum effective dose to produce 90\% paralysis (ED\(_{90}\)) of 1.15 mg kg\(^{-1}\) compared to an ED\(_{95}\) of 0.3 mg kg\(^{-1}\) for rocuronium.\(^5\)\(^-\)\(^8\) As a result, rapacuronium would be expected to have a more rapid onset and better intubating conditions at 60 s than other currently available non-depolarizing neuromuscular blocking drugs. Because the effect of neuromuscular blocking drugs is known to be influenced by the anaesthetic technique, the effect of the maintenance anaesthetic (volatile versus intravenous) on the recovery profile after rapacuronium-induced blockade must be examined.

This study was designed to test the hypothesis that standard intubating doses of rapacuronium and rocuronium differ with regard to their onset/offset of action and tracheal intubating conditions. In addition, we compared the initial recovery profiles of the two non-depolarizing neuromuscular blocking drugs during propofol- or sevoflurane-based anaesthesia.

Patients and methods

After obtaining institutional review board approval and written, informed consent, 60 ASA I-II patients aged 21–75 yr undergoing minor orthopaedic surgical procedures were enrolled in the study. Patients with hepatic, renal or neuromuscular disease, or those taking anticonvulsants, aminoglycoside or polypeptide antibiotics, or any other medication known to modify the action of neuromuscular blockers, were excluded from the study. Exclusion criteria also included body weight >130\% of ideal and anticipated difficulty in performing tracheal intubation.

On arrival in the operating room, the electrocardiogram (ECG), haemoglobin oxygen saturation (\(\text{S}_\text{PO}_2\)), and non-invasive arterial pressure were monitored. After premedica-
tion with midazolam 2 mg i.v., anaesthesia was induced with propofol 2.5 mg kg\(^{-1}\) and fentanyl 1.5 μg kg\(^{-1}\) i.v., followed 2 min later by either rapacuronium 1.5 mg kg\(^{-1}\) (n=30) or rocuronium 0.6 mg kg\(^{-1}\) (n=30) according to a computer-generated randomization sequence. One minute after administration of the neuromuscular blocking drug, direct laryngoscopy was initiated followed by tracheal intubation. Intubating conditions were assessed using a three-point scale (Table 1)\(^6\) by an experienced anaesthetist who was blinded to which neuromuscular blocking drug was administered. A 20-s interval was allowed for the first attempt at intubation, and in the event of failure, a second attempt was made at 90 s.

Anaesthesia was initially maintained with either a propofol infusion 100 μg kg\(^{-1}\) min\(^{-1}\) or 1% sevoflurane (end-tidal) according to random assignment, in combination with 66% nitrous oxide (N\(_2\)O) in oxygen using a semiclosed circuit with a total flow of 3 litres min\(^{-1}\) (n=15 in each subgroup). Incremental bolus doses of fentanyl were administered as required. Ventilation was controlled to maintain an end-tidal partial pressure of carbon dioxide (P\(_{\text{ETCO}_2}\)) between 4.3 and 5.5 kPa. A skin thermistor was taped to the hand close to the electromyographic (EMG) monitoring site. Skin temperature and central temperature (measured at the oesophagus) were maintained above 32.5°C and 36.5°C, respectively, using warmed blankets. End-expired partial pressures of carbon dioxide, nitrous oxide and sevoflurane were measured using a multiple gas analyser (Capnomac Ultima; Datex) which had been calibrated using a standard gas mixture (Quick Cal, Datex).

Neuromuscular monitoring was performed using the Datex Relaxograph (Helsinki, Finland) to record the EMG response of the adductor pollicis to supramaximal square-wave train-of-four (TOF) stimulation of the ulnar nerve at the wrist for 0.2 ms every 10 s during the onset period, and every 20 s following tracheal intubation. The EMG recording apparatus was connected to the patient before induction of anaesthesia, and the ‘baseline’ calibration sequence (which required 45–60 s to complete) performed as soon as the patient lost consciousness. This was followed 1 min later by a bolus dose of either rapacuronium or rocuronium, administered over 5 s into a rapidly flowing i.v. infusion line positioned in the contralateral forearm from that used for neuromuscular monitoring. Neuromuscular blockade was allowed to recover spontaneously until the first response to TOF stimulation (T\(_1\)) achieved at least 25% of the baseline value.

Clinically significant cardiovascular events (i.e. changes in arterial pressure or heart rate 30% above or below baseline values) occurring within 10 min of administration of the study drug and any possible histamine release-related signs (e.g. flushing, cutaneous erythema, bronchospasm) were recorded. An adverse event was defined as an unusual or unexpected clinical sign, which manifested itself or worsened during the intraoperative study period, irrespective of whether it was thought to be study drug related.

The following parameters were measured or calculated from the EMG recordings: (i) the time from the end of study drug injection until first depression T\(_1\) (lag time); (ii) the time from the end of study drug injection until 95% depression T\(_1\) (onset time); (iii) the degree of block at 60 s; (iv) the extent of maximum block; and (v) the time from the end of study drug injection until spontaneous recovery of T\(_1\)/T\(_0\) to 25%. The time to 25% recovery T\(_1\)/T\(_0\) was calculated by using the final EMG T\(_1\)/T\(_0\) value as a reference.\(^7\)

The sample size was determined by performing an \textit{a priori} power analysis to detect a difference of 30% or more in the onset time between the two neuromuscular blocking drugs (0.05 two-sided significance level, 80% power) based on previously published data.\(^1\) Analysis of variance (ANOVA) was used for analysing physical characteristics, and Fisher’s exact test was utilized for assessing intubating conditions and adverse effects. Student’s t-test or Mann–Whitney U-test was used for analysing onset and offset times between the two neuromuscular blocking drugs and the two anaesthetic techniques as appropriate. Differences between groups were considered statistically significant when the \(P\)-value was <0.05.

**Results**

The four subgroups were comparable with regard to age, weight, height, sex, ASA class and maintenance anaesthetic requirement (Table 2).

The lag times were similar after the two drugs but the onset time of rapacuronium was significantly shorter than that of rocuronium (Table 3). The degree of block at 60 s produced by rapacuronium was also greater than rocuronium (Table 3). Tracheal intubating conditions were comparable for both neuromuscular blocking drugs, with a
Table 2 Physical characteristics and anaesthetic drug requirements for the four study subgroups. Values are mean (SD or range), or numbers. No significant differences were noted between the four groups for any variable

<table>
<thead>
<tr>
<th></th>
<th>Rapacuronium (Propofol n=15)</th>
<th>Sevoflurane (n=15)</th>
<th>Rocuronium (Propofol n=15)</th>
<th>Sevoflurane (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>36 (21–70)</td>
<td>38 (21–63)</td>
<td>42 (29–68)</td>
<td>40 (22–75)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76 (15)</td>
<td>77 (16)</td>
<td>79 (11)</td>
<td>77 (18)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170 (9)</td>
<td>171 (11)</td>
<td>173 (13)</td>
<td>165 (13)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>9/6</td>
<td>8/7</td>
<td>9/6</td>
<td>8/7</td>
</tr>
<tr>
<td>ASA (1/2)</td>
<td>5/10</td>
<td>7/8</td>
<td>6/9</td>
<td>5/10</td>
</tr>
<tr>
<td>Propofol (µg kg⁻¹ min⁻¹)</td>
<td>108 (20)</td>
<td>—</td>
<td>105 (21)</td>
<td>—</td>
</tr>
<tr>
<td>Sevoflurane (end-tidal %)</td>
<td>—</td>
<td>1.1 (0.1)</td>
<td>—</td>
<td>1.1 (0.1)</td>
</tr>
</tbody>
</table>

Table 3 Onset and initial recovery variables as well as intubation conditions after rapacuronium 1.5 mg kg⁻¹ or rocuronium 0.6 mg kg⁻¹. Propofol + sevoflurane represents pooled data of the two subgroups. Values are mean (SD (median)), or numbers (percentages). *p<0.05, **p<0.001 vs rocuronium

<table>
<thead>
<tr>
<th></th>
<th>Rapacuronium</th>
<th>Rocuronium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lag time (s)</td>
<td>42 (11 (40))</td>
<td>44 (16 (45))</td>
</tr>
<tr>
<td>Onset time (s)</td>
<td>87 (20 (81))**</td>
<td>141 (65 (125))</td>
</tr>
<tr>
<td>Block at 60 s (%)</td>
<td>69 (26 (82))*</td>
<td>50 (27 (55))</td>
</tr>
<tr>
<td>Maximum block (%)</td>
<td>99 (2 (100))</td>
<td>98 (3 (100))</td>
</tr>
<tr>
<td>Intubating conditions at 60 s (n, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>16 (53)</td>
<td>14 (47)</td>
</tr>
<tr>
<td>Good</td>
<td>10 (33)</td>
<td>11 (37)</td>
</tr>
<tr>
<td>Poor</td>
<td>1 (3)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Impossible</td>
<td>3 (10)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Time to recovery of T₁/T₀ to 25% (min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>15.0 (3.2 (14.3))**</td>
<td>39.1 (14.2 (43.3))</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>15.1 (4.2 (15.0))**</td>
<td>47.8 (19.0 (40.5))</td>
</tr>
<tr>
<td>Propofol + sevoflurane</td>
<td>15.1 (3.7 (14.5))**</td>
<td>43.4 (16.8 (41.1))</td>
</tr>
</tbody>
</table>

Good-to-excellent rating achieved in 87% and 83% of patients at 60 s with rapacuronium and rocuronium, respectively (Table 3). Intubation was not possible in three (10%) patients in each group at 60 s due to inadequate muscle relaxation; however, they were successfully intubated at 90 s with an equal distribution of excellent, good and poor scores among the three patients in each group. Recovery of T₁/T₀ to 25% was similar for each neuromuscular blocking drug during propofol- or sevoflurane-based anaesthesia (Table 3). When compared with rocuronium, recovery of T₁/T₀ to 25% after rapacuronium was significantly shorter during both propofol- and sevoflurane-based anaesthesia (Table 3).

Adverse events were noted in five patients after rapacuronium and four patients after rocuronium. In the rapacuronium group, one case of severe bronchospasm was noted after tracheal intubation in a 35-year-old male smoker. The other adverse events (e.g. transient tachycardia or hypotension) occurred after tracheal intubation and administration of the maintenance anaesthetic. They required no treatment and were considered unlikely to be related to the study drugs.

Discussion

This study confirmed the rapid onset of neuromuscular block after rapacuronium 1.5 mg kg⁻¹ i.v.³,⁴ The lag time and extent of maximum block determined in our study were in agreement with those reported by van den Broek and colleagues (42 (11) vs 41 (13) s and 99 (2) vs 99 (1)% respectively),³ whereas the onset time and blockade at 60 s were similar to the findings of Debaene and colleagues (87 (20) vs 96 (20) s and 69 (26) vs 62 (31)%, respectively).⁴

The dose–response relationship for rapacuronium has not been well established. In their preliminary investigation, Wierda and colleagues² reported an ED₉₀ of 1.15 mg kg⁻¹ for rapacuronium. However, the dosage used was based on the bromide salt of rapacuronium, whereas the dosage calculation in the more recent studies was based on the free base (100 mg=113.4 mg of the bromide salt). Thus, a dose of rapacuronium 1.5 mg kg⁻¹ in our study would represent 1.5×ED₉₀ (recalculated for the free base). Our study demonstrated that even at this lower dose (1.5×ED₉₀ vs 2×ED₉₀), the onset of action was more rapid and the degree of blockade at 60 s greater with rapacuronium compared to rocuronium.

This finding is consistent with the inverse relationship between potency of non-depolarizing neuromuscular blocking drugs and the speed of onset of effect.⁵ With less potent drugs like rapacuronium, more drug molecules are administered, thereby increasing the concentration gradient between the plasma and the motor end-plate.⁹,¹⁰ An alternative explanation for the rapid onset of rapacuronium relates to its rapid equilibration between the plasma and
Rapacuronium versus rocuronium during propofol or sevoflurane anaesthesia

effect sites. The equilibration rate constant (Keo) of rapacuronium (0.41 min⁻¹) is more than twice that of rocuronium (0.17 min⁻¹) and 3.4 times that of vecuronium (0.12 min⁻¹). Additionally, in animal studies rapacuronium has been shown to possess calcium channel blocking effects that produce vasodilatation 25–50 times greater than vecuronium. Increased blood flow to skeletal muscle may also contribute to the rapid onset of neuromuscular blockade with rapacuronium.

The fast onset of neuromuscular blocking effect after rapacuronium coincides with the achievement of clinically acceptable (good-to-excellent) intubating conditions in the majority of patients at 60 s. Kahlwaji and colleagues reported good-to-excellent intubating conditions in 86% of young adults and 84% of elderly patients within 90 s after rapacuronium 1.5 mg kg⁻¹. However, our findings differed from those of Wierda and colleagues who reported good-to-excellent intubating conditions at 60 s in 100% of patients. A possible explanation for this difference relates to the fact that tracheal intubation was performed 5–10 min after inhalation of isoflurane (1.0%) in combination with nitrous oxide in the earlier study. The onset time of rapacuronium 1.5 mg kg⁻¹ in the laryngeal adductor muscles is 1.0 (0.2) min, shorter than rocuronium 0.5 mg kg⁻¹ at 1.4 (0.3) min and approaching succinylcholine 0.5 mg kg⁻¹ at 0.9 (0.1) min. At the time of intubation, rapacuronium-induced neuromuscular block at the larynx would be nearly maximum, thereby facilitating tracheal intubation.

The 25% recovery time of rapacuronium was found to be longer in the present investigation compared to two previous studies by Wierda and colleagues. These investigators reported that 25% T₁/T₀ recovery of rapacuronium was 8.0 (1.9) min and 8.9 (2.0) min during 1.0% isoflurane and 1.0% halothane anaesthesia, respectively. However, our results are consistent with those of Kahlwaji and colleagues (14 (6) min for young adults and 17 (5) min for elderly adults) and Purdy and colleagues (16.2 (4.0 min)). The discrepancies are probably accounted for by the different drug moieties. A dose of 1.5 mg kg⁻¹ in the present study is equivalent to 1.7 mg kg⁻¹ in Wierda’s studies, at least partially explaining the difference in 25% T₁/T₀ recovery time. Recovery time of T₁/T₀ to 25% after rapacuronium during either propofol- or sevoflurane-based anaesthesia was found to be significantly shorter than after rocuronium. The more rapid plasma clearance of rapacuronium contributes to its shorter duration of action (7.3 ml kg⁻¹ min⁻¹ vs 4.0 ml kg⁻¹ min⁻¹ for rocuronium). Recovery of T₁/T₀ to 25% with both neuromuscular blocking drugs was similar during propofol and sevoflurane anaesthesia. This finding may be related to the time-dependent potentiating effects of potent inhaled agents on non-depolarizing neuromuscular blocking drugs. Although data for sevoflurane are not available, full isoflurane-induced potentiation of muscle relaxant activity requires 30–45 min of steady-state anaesthesia. It is possible that the 25% recovery of T₁/T₀ after both rapacuronium and rocuronium would have been prolonged during sevoflurane (vs propofol) anaesthesia had the exposure occurred over a longer time interval. Xue and colleagues have reported that recovery of T₁/T₀ to 25% after rocuronium 0.4 mg kg⁻¹ was longer during sevoflurane anaesthesia (1.75%) compared to a propofol-based technique. However, in their study the patients received the volatile anaesthetic for ~40 min before the neuromuscular blocking drug was administered. The experimental design used by these investigators bears little relevance to the usual clinical situation; we therefore allowed for a much shorter stabilization period of ~1 min.

A shortcoming of the current study lies in the use of the Datex Relaxograph for monitoring neuromuscular function. As a result of the downward drift of the EMG amplitude over time, it is not uncommon for T₁/T₀ to regain only 70–80% of its baseline value despite a TOF ratio exceeding 0.9. In the present study, the final T₁/T₀ values recovered to 81 (SD 9)% of baseline values, corresponding to TOF ratios of ≧0.85. To compensate for this phenomenon, the values for 25% T₁/T₀ recovery times were determined by using proportional recalculation based on the final EMG T₁/T₀ value.

In conclusion, rapacuronium 1.5 mg kg⁻¹ exhibited a more rapid onset of action than rocuronium 0.6 mg kg⁻¹ and provided good-to-excellent intubating conditions in the majority of patients at 60 s. The initial recovery time of rapacuronium was ~50% shorter than that of rocuronium, and was not significantly altered by the maintenance anaesthetic. These data suggest that rapacuronium is a useful addition to the armamentarium of currently available non-depolarizing neuromuscular blocking drugs for facilitating tracheal intubation in patients undergoing short surgical procedures.

Acknowledgement
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References
4 Debaene B, Lieutaud T, Billard V, Meistelman C. ORG 9487 neuromuscular block at the adductor pollicis and the laryngeal adductor muscles in humans. Anesthesiology 1997; 86: 1300–5


7 Meretoja OA, Theroux M. Can final EMG baseline be used as a reference to calculate neuromuscular recovery. *Acta Anaesthesiol Scand* 1997; 41: 492–6


10 Kopman AF. Gallamine, pancuronium and d-tubocurarine compared: is onset time related to drug potency? *Anesthesiology* 1989; 70: 915–20


13 Fisher DM, Wright PM. Are plasma concentration values necessary for pharmacodynamic modeling of muscle relaxants? *Anesthesiology* 1997; 86: 567–75


