Comparison of intubating conditions after rapacuronium (Org 9487) and succinylcholine following rapid sequence induction in adult patients†

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We have assessed intubating conditions provided by rapacuronium (Org 9487) and succinylcholine after rapid sequence induction of anaesthesia in adult patients undergoing elective surgery. We studied 335 patients, ASA I and II, in five centres. Two hundred and thirty-four subjects with normal body weight and 101 obese subjects were allocated randomly to one of four treatment groups differing in the neuromuscular blocking drug administered (rapacuronium 1.5 mg kg\(^{-1}\) or succinylcholine 1 mg kg\(^{-1}\)) and in the technique used for induction of anaesthesia (fentanyl 2–3 \(\mu g\) kg\(^{-1}\) with thiopental 3–6 mg kg\(^{-1}\) or alfentanil 20 \(\mu g\) kg\(^{-1}\) with propofol 1.5–2 mg kg\(^{-1}\)). Intubation was started at 50 s by an anaesthetist blinded to the drugs used. Intubating conditions were clinically acceptable (excellent or good) in 89.4% of patients after rapacuronium and in 97.4% after succinylcholine (\(P<0.004\), the estimated difference being 8.1% (95% confidence interval (CI) 2.0–14.1%). Neither anaesthetic technique nor subject group had an influence on intubating conditions. After intubation, the maximum increase in heart rate averaged 23.1 (SD 25.4)% and 9.4 (26.1)% after rapacuronium and succinylcholine, respectively (\(P<0.001\)). Pulmonary side effects (bronchospasm and increased airway pressure) were observed in 10.7% (95% CI 5.8–17%) and 4.1% (95% CI 1.3–8.8%) of patients given rapacuronium and succinylcholine, respectively (\(P=0.021\)). We conclude that after rapid sequence induction of anaesthesia in adults, clinically acceptable intubating conditions were achieved less frequently after rapacuronium 1.5 mg kg\(^{-1}\) than after succinylcholine.

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Rapacuronium (Org 9487), in common with rocuronium, is an aminosteroidal neuromuscular blocking drug with a fast onset of action.\(^1,2\) In a previous, phase II clinical study, intubating conditions 60 s after rapacuronium 1.5 mg kg\(^{-1}\) (bromide salt, approximately 1.3 times its ED\(_{90}\)) were similar to those after succinylcholine 1 mg kg\(^{-1}\).\(^2\) Time to recovery from neuromuscular block (T\(_{1\text{N}}\) =90%) did not differ between rapacuronium, antagonized with neostigmine after 2 min, and succinylcholine (mean time 10.6 vs 11.6 min).\(^2\) Based on these results, rapacuronium may be considered to be a potential alternative to succinylcholine for tracheal intubation within 1 min and rapid recovery from block.

The purpose of this multicentre phase III study was to compare intubating conditions at 50 s provided by rapacuronium 1.5 mg kg\(^{-1}\) active moiety (i.e. free base, 1.5 times its ED\(_{90}\)) and by succinylcholine 1 mg kg\(^{-1}\) after rapid sequence induction of anaesthesia in adult patients undergoing elective surgery. In addition, adverse experiences and the cardiovascular response to intubation were assessed.

In contrast with the study of Wierda and colleagues,\(^2\) onset of neuromuscular block was not measured, as paralysis of the adductor pollicis muscle and intubating conditions may be poorly correlated.\(^3\) Moreover, maintenance of anaesthesia for several minutes, which is necessary during stabilization of the twitch response,\(^2,3\) interferes with the aim of assessing intubating conditions after rapid sequence induction.

†This article is accompanied by Editorial I
Patients and methods

After obtaining approval from the Ethics Committees of the five study centres and written informed patient consent, we studied 335 adult patients, ASA I and II, aged 18–65 yr, undergoing elective surgery under general anaesthesia. Two patient groups, 234 subjects with normal body weight (body mass index $\geq 18$ and $\leq 28$ kg m$^{-2}$) and 101 obese subjects (body mass index $\geq 30$ kg m$^{-2}$), were allocated randomly to one of four treatment groups that differed in the induction technique (thiopental with fentanyl or propofol with alfentanil) and the neuromuscular blocking drug (rapacuronium or succinylcholine) used. Randomization was stratified for subject group (subjects with normal weight and obese subjects) and study centre. Based on the preoperative physical examination, difficult intubation was not anticipated in any patient. None had a history of malignant hyperthermia or was receiving any medication known to interact with neuromuscular blocking agents. Pregnant patients were excluded.

Oral premedication with midazolam 7.5 mg or clorazepate 20–25 mg was administered at the discretion of the anaesthetist, 60–90 min before surgery. After 3 min of preoxygenation, anaesthesia was induced with thiopental 3–6 mg kg$^{-1}$ or propofol 1.5–2 mg kg$^{-1}$ followed by rapacuronium 1.5 mg kg$^{-1}$ active moiety (1.5 times its ED$_{90}$) or succinylcholine 1 mg kg$^{-1}$. Cricoid pressure was applied. Fentanyl 2–3 µg kg$^{-1}$ was administered 4 min before thiopental, and alfentanil 20 µg kg$^{-1}$ was given immediately before propofol. All drugs were injected into a rapidly running infusion of lactated Ringer’s solution. Injection times were 10 s for alfentanil and thiopental, 15 s for propofol, and less than 5 s for rapacuronium and succinylcholine.

In each centre, one fully trained anaesthetist, who was blinded to each patient’s treatment, performed all intubations using a Macintosh size 4 blade. A tracheal tube with an internal diameter of 8.0 mm in males and 7.0 mm in females was used. A flexible plastic mounted stylet was inserted into the tube. In order to prevent the intubator from noting succinylcholine-related muscle fasciculations, he was called into the study room not earlier than 45 s after administration of each neuromuscular blocking drug, and another 5 s later he was instructed to start intubation. Intubation time was recorded as the number of seconds from the end of administration of the neuromuscular blocking drug until insertion of the tracheal tube and cuff inflation, as measured by a stopwatch. Intubating conditions were evaluated as proposed by Viby-Mogensen and colleagues. Five factors were considered for assessment, that is, ease of laryngoscopy, position and movement of vocal cords, airway reaction and movement of limbs.

During the first 10 min after intubation, anaesthesia was maintained with 0.2–0.4% inspired isoflurane and 66% nitrous oxide in oxygen in the groups given thiopental and fentanyl for induction, or with propofol 150 µg kg$^{-1}$ min$^{-1}$ plus alfentanil 1 µg kg$^{-1}$ min$^{-1}$ in the two other groups. Thereafter, anaesthetic management was decided by the attending anaesthetist. Heart rate, non-invasive arterial pressure, arterial oxygen saturation (SaO$_2$) and end-tidal carbon dioxide concentration were assessed in all patients during the preoxygenation period (baseline) and during the first 10 min after administration of the neuromuscular blocking drug.

An adverse experience was defined as an unusual or unexpected sign, which manifested itself or worsened during the study, irrespective of whether or not it was thought to be drug-related. Investigators indicated whether they saw a link between the adverse effect and administration of rapacuronium.

Statistical analysis

Summary statistics were calculated for all quantitative variables in each group. Rates of clinically acceptable (excellent or good) and of excellent intubating conditions were calculated separately for rapacuronium and succinylcholine using two-sided 95% confidence intervals (CI). Intubation data were analysed using the Mantel–Haenszel test, with subject group and anaesthetic technique serving as stratification variables. The sample size was based on detecting a difference of 10% or more in the rate of clinically acceptable intubating conditions between the two neuromuscular blocking drugs (0.05 two-sided significance level, 80% power), assuming an acceptable rate of 96% with succinylcholine. Changes in heart rate (HR) and mean arterial pressure (MAP) after intubation were analysed using two-way repeated measures ANOVA, with induction technique and neuromuscular blocking drug as the two relevant factors. Analysis within groups was performed using a paired Student’s $t$ test, and between-group comparisons using one-way ANOVA. Bonferroni correction for multiple comparisons was applied. Calculations were carried out using SYSTAT 7.0 (SPSS Inc., Chicago, USA) or SAS Version 6.08 (SAS Institute, Cary, NC, USA).

Results

We studied 335 patients. Median age was 35 (range 18–63) yr in subjects with normal body weight ($n=234$) and 41 (range 20–64) yr in obese subjects ($n=101$). Mean body mass index in normal and obese subjects was 23.7 (SD 2.4) kg m$^{-2}$ and 34.2 (4.8) kg m$^{-2}$, respectively. Males predominated in the group with normal body weight (77.8%), whereas in the group of obese patients they accounted for only 47.5% ($P=0.001$). Nineteen patients were excluded because of major protocol violations (i.e. incorrect dose of neuromuscular blocking drug ($n=8$), incorrect body mass index ($n=5$), incorrect induction technique ($n=4$), paravenous injection ($n=1$) and pregnancy ($n=1$)).

The rates of clinically acceptable (excellent or good) and of excellent intubating conditions were significantly higher.
after succinylcholine than after rapacuronium (Table 1). Intubating conditions were not influenced by the anaesthetic technique or subject group. The frequency distributions of intubating conditions were analysed for pooled data of subjects with normal body weight and obese subjects, and for both anaesthetic techniques. The results of the intention-to-treat analysis and the per-protocol analysis did not differ. In three patients (one after rapacuronium and two after succinylcholine) the initial attempt at intubation failed because of unexpected difficulties in laryngoscopy or incomplete paralysis. Intubating conditions in these patients were rated as poor. Intubation time did not differ between rapacuronium and succinylcholine (mean 63.9 (so 8.3) s).

Of the five variables contributing to the assessment of intubating conditions, laryngoscopy was judged to be easy, fair and difficult in 80.6%, 18.8% and 0.6% of patients after rapacuronium, and in 90.4%, 7.7% and 1.9% after succinylcholine (P=0.01). On laryngoscopy, vocal cords were abducted, in the intermediate position and closed in 79.4%, 18.7% and 1.9% of cases after rapacuronium, and in 91.7%, 7.7% and 0.6% after succinylcholine (P=0.008); the vocal cords were immobile, moving and closing in 90.6%, 6.3% and 3.1% of patients after rapacuronium, and in 96.2%, 3.2% and 0.6% after succinylcholine (P=0.11). The response to insertion of the tracheal tube and cuff inflation was more marked after rapacuronium. No coughing, movement of the diaphragm or sustained coughing were observed in 66.2%, 28.1% and 5.6% of patients given rapacuronium, and in 87.8%, 11.5% and 0.6% given succinylcholine (P<0.001). Movement of the limbs in response to intubation was absent, slight and vigorous in 85.0%, 11.9% and 3.1% of patients given rapacuronium, and in 91.0%, 8.4% and 0.6% given succinylcholine (P=0.14).

Median doses of thiopental and propofol were 5.65 (range 3.6–7.4) mg kg⁻¹ and 2.0 (1.0–2.5) mg kg⁻¹, respectively. Median doses of fentanyl and alfentanil were 2.1 (0.7–3.2) µg kg⁻¹ and 20.0 (15.0–24.6) µg kg⁻¹. Anaesthetic technique (P=0.01) and neuromuscular blocking drug (P<0.01) had a significant influence on changes in HR and MAP after rapid sequence induction of anaesthesia. After intubation, the maximum increase in HR averaged 23.1 (so 25.4)% after rapacuronium and 9.4 (26.1)% after succinylcholine (P<0.001). HR and MAP responses to tracheal intubation in the four treatment groups are summarized in Table 2.

Eighteen cases of pulmonary side effects (14 cases of bronchospasm and four cases of increased airway pressure) were observed after rapacuronium (10.7% of patients, 95% CI 17.0%), and seven cases of bronchospasm after intubation facilitated by succinylcholine (4.1% of patients, 95% CI 1.3–8.3%) (P=0.021). One case of bronchospasm, probably related to rapacuronium, was reported to be a serious adverse experience. This occurred in a patient with a medical history of chronic bronchitis but clear lungs on auscultation on the day before surgery. The episode of bronchospasm started immediately after intubation and gradually subsided under isoflurane anaesthesia and after administration of theophylline, feneterol and prednisolone. The minimum arterial oxygen saturation over a period of 5 min on oxygen 100% was 88%.

**Discussion**

The results of our study indicate that clinically acceptable (excellent or good) intubating conditions were achieved less frequently after rapacuronium 1.5 mg kg⁻¹ (1.5 times its ED₉₀) than after succinylcholine 1.0 mg kg⁻¹ following rapid sequence induction of anaesthesia in adult patients undergoing elective surgery. However, the anaesthetic technique used for induction of anaesthesia (i.e. fentanyl–thiopental or alfentanil–propofol) had no significant influence on intubating conditions at 50 s after rapacuronium. In addition, there was no difference in the incidence of clinically acceptable intubating conditions between patients with normal body weight and obese patients. In the latter, particularly in morbidly obese patients (i.e. body mass index >35 kg m⁻²), rapid tracheal intubation is indicated even in elective cases because of reduced alveolar oxygen reserves.

The findings of our study are not consistent with those of Wierda and colleagues who used slightly lower doses of rapacuronium (i.e. approximately 1.3 times its ED₉₀). In that study, intubating conditions at 60 s were similar to those after succinylcholine. However, intubation was performed approximately 5–10 min after induction of anaesthesia with thiopental and fentanyl, and after calibration of the relaxometer under isoflurane-nitrous oxide anaesthesia, conditions quite different from rapid sequence induction. Similar results to ours were reported by Kahwaji and colleagues, who assessed the time course of action and intubating conditions using five different doses of rapacuronium (0.5, 1.0, 1.5, 2.0 and 2.5 mg kg⁻¹). In that study,
anaesthesia was induced with thiopental 3–6 mg kg\(^{-1}\) and fentanyl, followed by a short stabilization period of less than 3 min. Good to excellent intubating conditions were achieved in 86% of adults and 84% of elderly patients within 90 s after doses of rapacuronium equal to, or greater than, 1.5 mg kg\(^{-1}\).\(^5\)

Adequate relaxation of the laryngeal muscles and diaphragm is required to obtain excellent intubating conditions. In our study, the position of the vocal cords was less favourable after rapacuronium than after succinylcholine, which may be a result of incomplete neuromuscular block at the intrinsic laryngeal muscles.\(^6\) The ED\(_{90}\) of rapacuronium at the laryngeal muscles was estimated to be approximately 2.0 mg kg\(^{-1}\), which is about twice the ED\(_{90}\) of this neuromuscular blocking drug at the adductor pollicis muscle.\(^6\) The relative resistance of the vocal cords to the effects of neuromuscular blocking drugs has also been demonstrated after rocuronium and other non-depolarizing neuromuscular blocking drugs.\(^7\) The response to insertion of the tracheal tube was more marked after rapacuronium than after succinylcholine; movement of the diaphragm and sustained coughing were observed more frequently. The use of higher doses of rapacuronium may be necessary to achieve complete block at the laryngeal adductor muscles\(^6\) or to avoid coughing in response to intubation, if this is essential. Higher doses of rapacuronium, however, prolong its duration of action. The clinical duration (duration 25%) of rapacuronium 2.0 mg kg\(^{-1}\) and 2.5 mg kg\(^{-1}\) averaged 18 min and 25 min, respectively, under i.v. anaesthesia.\(^5\)

A second aim of our study was to assess adverse experiences and the cardiovascular response during rapid sequence induction of anaesthesia. Pulmonary side effects (bronchospasm or increased airway pressure) occurred more frequently after rapacuronium than after succinylcholine. HR increased by an average of 11% in patients who were given rapacuronium after induction with alfentanil and propofol and by an average of 36% in patients who were given rapacuronium after induction with fentanyl plus thiopental. This clinically relevant increase in HR may be a result of both the specific effects of rapacuronium and the haemodynamic response to laryngoscopy and tracheal intubation. A dose of fentanyl equal to that used in this study was shown to attenuate MAP and HR responses to intubation, whereas only alfentanil 15 µg kg\(^{-1}\) prevented such a response.\(^8\) \(^9\) The slight decrease in MAP after rapacuronium observed in this study is similar to that described previously.\(^10\) Rapacuronium is an aminosteroidal neuromuscular blocking drug of low potency. There is evidence that the incidence of cardiovascular side effects of aminosteroidal neuromuscular blocking drugs increases with decreasing potency as a result of vagolytic effects, calcium channel blocking properties and probably non-immunological histamine release.\(^11\)–\(^13\) The observed side effects of rapacuronium (tachycardia, hypotension and bronchospasm) may be dose-related and warrant further attention in future studies.

In our study, two different induction regimens were used (i.e. fentanyl–thiopental and alfentanil–propofol). Assuming that alfentanil is 10–20% as potent as fentanyl,\(^14\) the specific opioid effect was less intense in patients given fentanyl than in patients given alfentanil. In addition, considering median induction doses, the effective dose of thiopental was higher than that of propofol.\(^15\) However, the peak effect of both fentanyl and alfentanil should have been reached at the time of intubation, as apparent concentrations of fentanyl and alfentanil peak at the site of action 3.6 min and 1.4 min, respectively, after a bolus dose.\(^16\) Despite these possible differences in the effective dose of the induction agents, intubating conditions were not influenced by the anaesthetic technique; they were, however, influenced by the neuromuscular blocking drug used.

In summary, 50 s after rapacuronium 1.5 mg kg\(^{-1}\) (1.5 times its ED\(_{90}\)) clinically acceptable intubating conditions were achieved less frequently than after succinylcholine after rapid sequence induction of anaesthesia in adults given either fentanyl–thiopental or alfentanil–propofol. The use of higher doses of rapacuronium may be necessary in order to achieve tracheal intubation within 1 min under intubating conditions similar to those after succinylcholine.

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