

Dose–Response and Onset/Offset Characteristics of Rapacuronium

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Background: **A rigorous study of the dose–response relation of rapacuronium has, to our knowledge, yet to be performed. In addition, there is little information available regarding the onset or offset profile of rapacuronium when administered in subparalyzing doses. These issues necessitate further study.**

Methods: **Forty-seven adult patients, American Society Anesthesiologists physical status I or II, were studied. Tracheal intubation was accomplished without muscle relaxants. Anesthesia was maintained with use of nitrous oxide, propofol, and alfentanil. The electromyogram of the first dorsal interosseous muscle was measured using a monitor. Single stimuli at 0.10 Hz were administered. A single dose of rapacuronium was administered. After log-dose or logit transformation of the data, the best-fit line of regression was determined using the method of least squares. For each subject, the authors estimated the 50% effective dose (ED_{50}) and 95% effective dose (ED_{95}) from the Hill equation using the slope obtained from regression analysis. The onset times to 50 and 90% of peak effect were estimated in a subset of 10 individuals in which peak twitch depression decreased to the range of 90–99%.**

Results: **The calculated ED_{50} and ED_{95} values for rapacuronium were 0.39 ± 0.08 (SD) and 0.75 ± 0.16 mg/kg, respectively. After a single ED_{95} dose, 90% of the drug's peak effect was evident in 77 ± 17 s. After this dose, rapacuronium has a clinical duration of 6.1 ± 1.1 min.**

Conclusions: **The authors found the ED_{95} of rapacuronium to be substantially less than suggested by previous estimates. Rapacuronium has an onset profile that is not different from that previously reported for succinylcholine. The rate of spontaneous recovery was faster after rapacuronium than the authors previously observed after mivacurium administration but was slower than after succinylcholine, using an identical protocol. (Key words: Potency; recovery.)**

RAPACURONIUM is a new aminosteroidal nondepolarizing neuromuscular blocking drug with a rapid onset and a short duration of action. Wierda *et al.* cite a 90% effective dose (ED_{90}) for the drug of 1.15 mg/kg (bromide salt). Assuming that the dose–response relation of the drug is not greatly different from other commonly used relaxants, this would translate into a 95% effective dose (ED_{95}) of approximately 1.35 mg/kg. Because the package labeling of the commercial product refers only to the active moiety (the base of the salt), the estimates of Wierda *et al.*[1] of the potency of rapacuronium should be reduced by 12% (to an ED_{95} of 1.19 mg/kg). However, at least one preliminary dose-ranging study (n = 10) presents data that suggest that the ED_{95} may be at little as 0.75 mg/kg.[2] Despite the recent approval of rapacuronium by the Food and Drug Administration, the 1994 article by Wierda *et al.*[1] is the only study of which we are aware that has attempted to quantify the ED_{90} value of rapacuronium. In addition, there is little information regarding the onset or offset profile of rapacuronium when administered in subparalyzing doses. Because these issues are of theoretical and practical interest, we decided that they needed further study.

Materials and Methods

Forty-eight adult patients (American Society of Anesthesiologists physical status I or II, aged 18–61 yr) undergoing elective surgical procedures were included in the study. All patients were free from neuromuscular disease and had a body mass index not less than 17.5 kg/m^2 nor greater than 27.5 kg/m^2. The protocol was approved by the Human Subject Review Committee of St. Vincent's Hospital and Medical Center, and informed consent was obtained. Anesthesia was induced with administration of 40 μg/kg alfentanil plus 2.0–2.5 mg/kg intravenous propofol, and tracheal intubation was accomplished without the use of muscle relaxants. Anesthesia was maintained with nitrous oxide (65–70% inspired) and propofol 50–75 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Ventilation was controlled, and end-tidal pressure of carbon dioxide (P_{CO_2}) was maintained between 34–40 mmHg.

The indirectly evoked integrated compound action potential of the first dorsal interosseous muscle to supramaximal stimulation of the ulnar nerve at the wrist was measured and recorded using an NMT 221 monitor (Datex, Tewksbury, MA). Single stimuli at 0.10 Hz were administered during the period of observation, and twitch depression was continuously recorded. Control twitch height was established after a 15- to 20-min period of baseline stabilization. Immediately after baseline calibration, a single dose of rapacuronium was administered.

The first subject received a bolus dose of rapacuronium (0.35 mg/kg). This dose was selected to approximate what we anticipated to be the 50% effective dose

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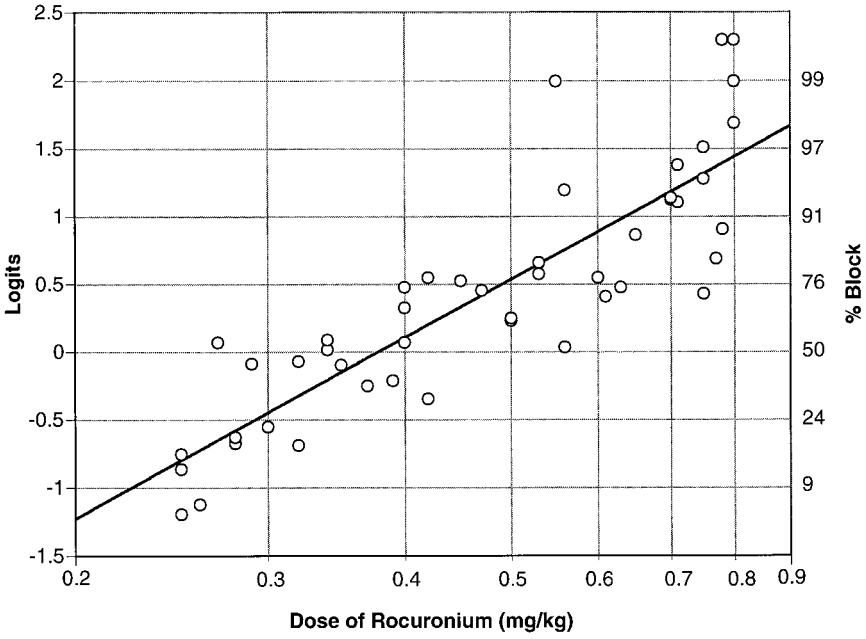

Fig. 1. Dose (log-scale) or logit plot of the dose–effect relation for rapacuronium. Percent twitch depression plotted on second *y* axis. When plotted as log-dose *versus* logit, $y = 4.43 \cdot x + 1.876$; $R^2 = 0.744$.

(ED_{50}). Using the Hill equation (with a postulated slope of 4.50), the ED_{50} was calculated for this patient. The second subject was administered a dose that equaled the calculated ED_{50} for patient 1. Patients 3–5 were administered a dose that approximated the average estimated value of the ED_{50} from the previously studied patients in this series. In a similar manner, patients 6–10 were administered a dose calculated to achieve 20% twitch depression. The next five subjects were administered doses that approximated the average estimated value of the ED_{80}. In the remaining patients, doses of rapacuronium were selected to provide almost equally distributed increments in the range estimated to span responses from 15 to 95% twitch depression.

In 10 patients, peak twitch depression ranged from 93 to 99%. The onset times to 50 and 90% of peak effect was estimated for this subset of subjects by use of interpolation. In these individuals, twitch height was recorded for 8 min so that the pattern of recovery from rapacuronium could be compared with our previous observations of succinylcholine and mivacurium, which were obtained using an identical protocol.[3]

Statistics

The dose–response relation of rapacuronium was calculated using methods previously described.[4] After log-dose or logit transformation of the data, the best-fit line of regression was determined using the method of least squares. Complete twitch depression was plotted as an effect of 99.5%. The coefficient of determination (R^2), slope, and standard error of the estimate of X (log-dose) were calculated using the Data Analysis Tools package included with Excel 98 for the Macintosh computer (all: Microsoft, Redmont, WA). ED_{50} and ED_{95} values were then estimated from the calculated line of regression. For each subject, the estimated ED_{50} and ED_{95} were also computed from the Hill equation using the slope previously calculated by regression analysis. The arithmetic mean and SD of these individual values were then determined.

Onset times to 50 and 100% of peak effect, and the clinical duration of neuromuscular block, were compared with values we previously observed for succinylcholine and mivacurium using an identical protocol.[3] These mean values were compared using an unpaired Student *t* test. The Bonferroni correction for two comparisons was applied. Observed differences were considered to be significant if $P < 0.05$.

Results

Forty-seven women were studied. Average age was 39.5 ± 11 yr. Average body mass index was 22.7 ± 1.9 kg/m^2. Administered doses of rapacuronium ranged from 0.25 to 0.80 mg/kg. No patients were excluded from analysis because of protocol violations. Responses ranged from 9 to 100% twitch depression. One hundred percent block occurred in two patients (after administration of doses of 0.78 and 0.80 mg/kg).

Using conventional linear regression analysis, the calculated best-fit line of regression (log-dose or logit plot) had a slope of 4.43, with a coefficient of determination (R^2) of 0.74 (fig. 1). Using this slope, when individual ED_{50} or ED_{95} values were estimated from the Hill equation, the average ED_{50} and ED_{95} values were 0.39 ± 0.08 (SD) and 0.75 ± 0.16 mg/kg, respectively (table 1). Calculated ED_{50} values for individual subjects varied within a threefold range (0.20–0.60 mg/kg), as did ED_{95} values (0.38–1.16 mg/kg). These ED_{50} and ED_{95} values

Table 1. Potency Data and Onset–Offset Characteristics of Rapacuronium

Potency*	
ED_{50} (mg/kg)	0.39 ± 0.0.8
	95% CL (0.23 to 0.54)
ED_{95} (mg/kg)	0.75 ± 0.16
	95% CL (0.45 to 1.06)
Onset†	
Seconds to 50% of peak effect	53 ± 4
Seconds to 90% of peak effect	77 ± 17
Seconds to peak effect	117 ± 23
Offset†	
T_1 (% control) at 5 min	16 ± 7
T_1 (% control) at 8 min	54 ± 17
Bolus to T_1 = 25% (min)	6.1 ± 1.1

Data are ± SD.

* N = 47.

† N = 10. Data from subjects in whom initial bolus achieved 90–99% twitch (T_1) depression.

CL = confidence limits.

did not differ significantly from those obtained using linear regression analysis (ED_{50} = 0.38 ± 0.10; ED_{95} = 0.74 ± 0.17).

In the subset of 10 subjects in whom 90–99% twitch depression was desired, the actual range of responses was 93–99% T_1 depression (mean = 95.7 ± 2.5 [SD]). Peak neuromuscular effect occurred within approximately 2 min, with 90% of that effect apparent within less than 90 s. By 5 min, some degree of recovery was always apparent, and T_1 was usually back to 50% of control 8 min after bolus administration (fig. 2; table 1). The clinical duration (bolus to T_1 = 25% of control) was 6.1 ± 1.1 min. The onset time to 90 and 100% of peak effect was not different from values we previously observed after succinylcholine (1 times the ED_{95}), but offset 5 min after drug administration was significantly slower.[3] Compared with mivacurium, onset time and clinical duration were significantly shorter after administration of rapacuronium.

Discussion

Although rapacuronium is available for clinical use in the United States, remarkably little quantitative information has been published regarding its potency in humans. A large percentage of the investigations of the pharmacodynamic actions of rapacuronium have dealt with evaluation of intubation conditions after the administration of doses far in excess of what we believe to be the ED_{95}.[5,6] We agree with previous reports that rapacuronium is a short-acting, nondepolarizing, neuromuscular blocking drug of low potency. The ED_{50} is more than twice the value we previously determined for rocuronium.[4] Nevertheless, our data suggest that the drug is more potent than early reports[1] indicate. The report of Wierda *et al.*[1] in 1994 of an ED_{90} of 1.01 mg/kg for the active moiety should be viewed as a dose-ranging rather than a classic dose–response study. Wierda *et al.* used their first six patients to estimate the ED_{90} dose by administering the drug using a cumulative dose technique. This method is almost guaranteed to underestimate the potency of a short- or ultrashort-acting blocker.[7–9] They then administered to an additional 10 patients the same single dose of rapacuronium (1.0 mg/kg). The authors made no attempt to estimate the ED_{50} of the drug. Therefore, although the results of Wierda *et al.*[1] are widely cited, we believe our observations are more likely to be correct.

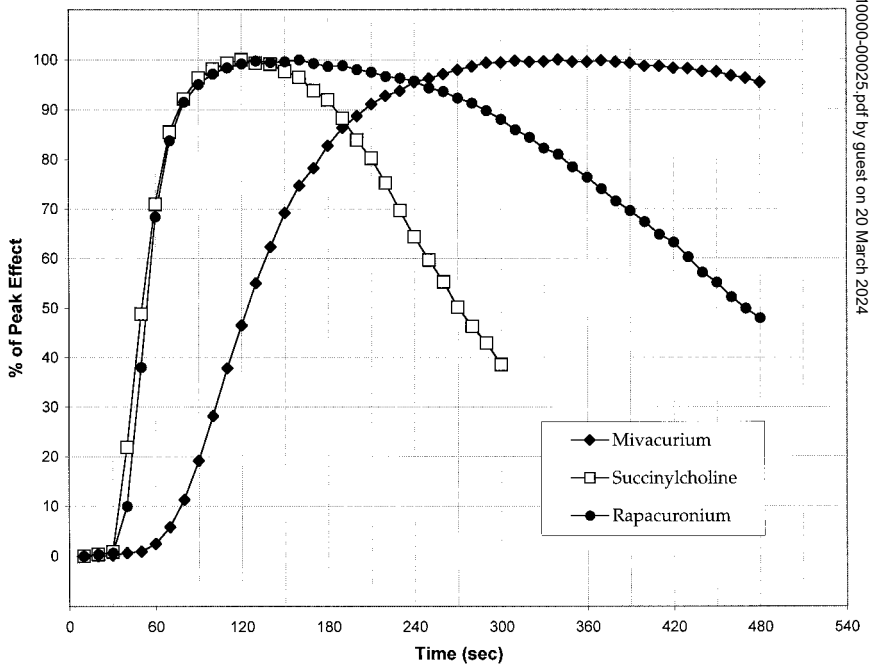

Fig. 2. Percent of peak effect after a single ED_{95} dose of succinylcholine, rapacuronium, or mivacurium as a function of time (n = 10 for all groups). The time to 90 and 100% of peak effect of rapacuronium and succinylcholine are not statistically different.

We calculate an ED_{95} value of 0.75 mg/kg. Therefore, the recommended "intubation dose" of 1.5 mg/kg is 2 times the ED_{95} dose. The slope (log-dose/logit) of the dose–response relation for rapacuronium (4.43) is not greatly different from what we expect with other neuromuscular blocking drugs.[3]

In evaluating our dose–response data, two special circumstances should be noted: (1) All subjects were women (n = 47). (2) There is some evidence to suggest that nondepolarizing blockers may be more potent on a milligram/kilogram basis in women than in men.[10] In addition, we took considerable effort to establish stable monitoring conditions before rapacuronium was administered. On average, almost 20 min elapsed between induction of anesthesia and drug administration. Marked peripheral vasodilatation usually is observed during this time period, and skin and muscle temperature of the hand may increase by as much as 5°C.[11,12] Presumably, this increase in temperature reflects an increase in muscle perfusion and skin blood flow. Therefore, drug delivery to the muscles of the hand will be enhanced during these conditions. This should result in higher peak drugs levels at the effector site of action. As a consequence, a dose found to produce 95% twitch depression at the adductor pollicis after 20 min of nitrous oxide–propofol–opioid anesthesia may result in a lesser degree of block (at the hand) when administered immediately after induction of anesthesia.

As expected from its low potency, rapacuronium has an onset profile that rivals that of succinylcholine. After administration of a single ED_{95} dose, the time to peak effect is approximately 2 min, and 90% of that effect is accomplished within approximately 80 s.

The recovery profile of rapacuronium appears to be dose-dependent and is distinctly different from that of mivacurium. After a single ED_{95} dose, the initial rate of T_1 recovery after rapacuronium was found to be significantly more rapid than previously observed after mivacurium administration (but longer in duration than after succinylcholine) using an identical protocol (fig. 2).[3] After this dose, the clinical duration of rapacuronium is approximately 6 min. Succinylcholine (1 times the ED_{95}) has a clinical duration of slightly less than 4 min, whereas, After mivacurium, T_1 is still only 10% of the control time at 8 min (at which time observations were no longer recorded).

However, as larger multiples of an ED_{95} dose are administered, the faster rate of recovery of rapacuronium, *vis-a-vis* mivacurium, begins to disappear. After a dose of 1.5 mg/kg, Miguel *et al.*[13] found the clinical duration of rapacuronium (bolus to T_1 = 25% of control) was approximately 15 min, with a 25–75% recovery interval of approximately 8 ± 5 min. An intubating dose of mivacurium (0.25 mg/kg, 3 times the ED_{95}) was found to have a clinical duration of 21 ± 5 min, a recovery interval of 8.8 ± 5 min, and a time to a train-of-four (TOF) ratio more than 0.80 of 34 ± 8 min. Therefore, at 1.5 mg/kg, the clinical duration of rapacuronium is shorter than that observed after administration of 0.25 mg/kg mivacurium, but the times to 70–80% TOF recovery are similar. When the dose of rapacuronium is increased to 2.5 mg/kg (≈ 3 times the ED_{95}), the recovery interval increases to 13 ± 9 min, with a clinical duration of 25 ± 10 min, and spontaneous recovery to a TOF ratio more than 0.80 may take more than 1 h (73 ± 25 min). Consequently, at equipotent 3 times the ED_{95} doses, the clinical duration of rapacuronium is somewhat longer than that of mivacurium ($P < 0.05$), and the time necessary for spontaneous return of the TOF ratio to clinically acceptable levels may exceed that seen after mivacurium administration by 30–40 min or more. This is not totally unexpected. The lower clearance of the active metabolite of rapacuronium, Org 9488, will gradually prolong the time course of the neuromuscular blockade during maintenance with rapacuronium.[14]

Wierda *et al.*,[15] in one of the earliest clinical reports of rapacuronium, reported that, combined with neostigmine administered 2 min after a modest initial dose of rapacuronium (1.3 times the ED_{90}), the bolus to recovery interval was similar to that seen with succinylcholine. They suggested that rapacuronium plus rescue reversal might make rapacuronium a "suitable candidate to replace succinylcholine."[15] Subsequent investigators who attempted to reverse the neuromuscular effects of larger doses (1.5–2.5 mg/kg) 2 to 5 min after administration have been less enthusiastic about this proposition.[16] Even with smaller doses of rapacuronium, Purdy *et al.*[17] found that 15–20 min was necessary before the TOF ratio returned to a value more than 0.70 after neostigmine-induced recovery.

Nevertheless, Wierda *et al.*[15] may have made a reasonable proposal. Because the spontaneous clinical duration of rapacuronium after 1 times the ED_{95} dose averages only 6 min, it is likely that attempted reversal 5 min after rapacuronium administration will be successful if the initial dose of blocker is less than 1.0 mg/kg. The clinical usefulness and ease of antagonism of this dose of rapacuronium deserves further study.

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