

Rapid Tracheal Intubation with Rocuronium

A Probability Approach to Determining Dose

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Background: Rapid tracheal intubation with rocuronium has not been studied using a probability-based approach. The authors aimed to predict doses of rocuronium giving 90% and 95% probability of intubation within 60 s and to estimate their durations of action.

Methods: After premedication with midazolam, 2 mg, anesthesia was induced in 80 subjects with fentanyl, 2 µg/kg, followed 3 min later by propofol, 2 mg/kg. Patients received randomly rocuronium, 0.0, 0.4, 0.8, or 1.2 mg/kg (n = 20/dose). Laryngoscopy began 40 s later, aiming for intubation at 60 s, and conditions were graded perfect, acceptable, or unacceptable, with the first two conditions being successful intubation. Anesthesia was maintained with isoflurane 0.5–1.0% (end-tidal) and fentanyl. Duration of action was time until reappearance of the first tactile train-of-four response. The dose *versus* fraction of patients with successful intubation was analyzed by logistic regression. Doses giving 90% and 95% (D₉₀ and D₉₅) probability of successful intubation were calculated.

Results: Intubation was successful in 7, 11, 18, and 19 patients in the 0.0, 0.4, 0.8, and 1.2 mg/kg groups, respectively. The D₉₀ and D₉₅ doses (95% confidence limits in parentheses) were 0.83 (0.59–1.03) and 1.04 (0.76–1.36) mg/kg, respectively. Estimated time until first tactile train-of-four response after D₉₀ and D₉₅ doses was 32 and 46 min, respectively.

Conclusions: After induction with fentanyl and propofol, rocuronium, 1.04 mg/kg, gives 95% probability of successful intubation at 60 s. (Key words: Anesthesia; neuromuscular blocking drug; neuromuscular function monitoring.)

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ROCURONIUM is the only approved nondepolarizing neuromuscular blocking drug with a rapid onset of action,¹ and as such it has been used to facilitate rapid tracheal intubation.^{2–4} The doses of rocuronium used in previous studies of rapid tracheal intubation have ranged from 0.6 to 1.2 mg/kg.^{2,3,5–7} In all these previous studies, predetermined doses of rocuronium were administered, and the incidence of successful intubation was reported. Such a study design gives information only about the particular doses administered but does not allow for prediction of the effect of doses that were not studied. In this study we took a different, probability-based approach. With this approach we can predict the effects of different doses of rocuronium, even if those specific doses were not administered. For example, we can predict the minimum dose required for a given probability of successful intubation and estimate the likely duration of action of that dose. This information would aid the clinician in the decision-making process involved in choosing an appropriate dose of rocuronium. Thus, our aim in the present study was to determine the doses of rocuronium that would give 90% and 95% probabilities of successful tracheal intubation within 60 s after rocuronium administration, and to estimate the durations of action of these doses.

Methods

The study was approved by our local institutional review board, and written informed consent was obtained from all patients. We studied 80 adults with American Society of Anesthesiologists physical status I or II admitted for elective surgical procedures. Patients aged more than 60 yr or less than 18 yr, having gastroesophageal reflux, weighing more than 30% more than ideal body weight, suffering from neuromuscular disease, or undergoing treatment with drugs known to interfere with neuromuscular transmission were excluded. All patients enrolled had Mallampati class 1, 2, or 3 airway anatomy

Table 1. Grading Criteria for Intubation Conditions

Criterion	Perfect	Acceptable	Unacceptable
Vocal cord position	Abducted	Intermediate	Adducted
Vocal cord movement	None	Moving	Closing
Ease of laryngoscopy	Jaw relaxed	Jaw resistant	Jaw very tight
Airway reaction	None	Transient	Sustained > 5 s
Movement of limbs	None	Slight	Vigorous

and no anticipated difficulty with mask ventilation or tracheal intubation.

Patients were premedicated with intravenous midazolam, 2 mg, before being transported to the operating room and within 15 min of the induction of anesthesia. In the operating room, routine monitoring of blood pressure, electrocardiogram, and pulse oximetry was initiated. Preoxygenation with 100% oxygen was performed for 3 min. Fentanyl, 2 $\mu\text{g}/\text{kg}$, was administered at the start of the preoxygenation procedure, and propofol, 2 mg/kg, was given to induce anesthesia. When the patient lost consciousness after the propofol administration, he or she was given intravenous rocuronium in a dose of 0.0, 0.4, 0.8, or 1.2 mg/kg, diluted in normal saline solution to a total volume of 15 ml. The dose each patient received was decided on a random basis by the selection of an unmarked envelope containing details of the dose. Twenty patients received each dose of rocuronium.

At 40 s after injection of the rocuronium or saline solution control, laryngoscopy was initiated, with the goal being to have the endotracheal tube passed through the patient's vocal cords and the cuff inflated within the following 20 s. If the endotracheal tube was not passed successfully within 30 s, *i.e.*, 70 s after rocuronium or saline solution administration, this was recorded as a failed intubation. All intubations were performed by one of the three authors, and the intubating conditions were graded perfect, acceptable, or unacceptable according to the criteria outlined in table 1.⁸ The investigator performing the intubation and assessing the conditions was blinded to the dose of rocuronium administered.

After tracheal intubation, anesthesia was maintained with isoflurane, 0.5–1.0%, nitrous oxide, 60–70% (end-tidal concentrations), and fentanyl boluses as required. Mechanical ventilation was adjusted to maintain the end-tidal carbon dioxide partial pressure at 30–35 mmHg. The patients' core temperatures were kept above 35.5°C by forced air warming.

Before induction of anesthesia, surface electrodes were placed over the ulnar nerve at the wrist. When the patient lost consciousness, train-of-four (TOF) stimulation (at 2 Hz and repeated every 12 s) was commenced. Immediately after tracheal intubation and every 5 min thereafter the investigator who performed the intubation counted the number of tactile TOF responses. The duration of action of rocuronium was defined as time from end of injection of rocuronium or saline control until reappearance of first tactile response to TOF stimulation.

Demographic characteristics in the four dosage groups were compared by analysis of variance or chi-square analysis as appropriate. Logistic regression was used to analyze the dose–response curve.⁹ The response was the fraction of patients with successful intubation (defined as either acceptable or perfect intubation conditions) at each dose of rocuronium. For the saline solution control group, the dose was entered as 0.0001 to permit logarithmic transformation. The equation used for the logistic regression was in the form: fraction of successful intubations = $P_3 + (1 - P_3)(A/[A + 1])$, where A is $\text{EXP}(P_1 + P_2[\log\text{dose}])$, and P1, P2, and P3 are the parameters of the model. The parameter P3 estimates the fraction of intubations that are successful if rocuronium dose is zero. The doses of rocuronium that gave a 50%, 90%, and 95% probability of successful intubation (D_{50} , D_{90} , and D_{95} , respectively) were then calculated.

To obtain confidence limits for the estimates of D_{50} , D_{90} , and D_{95} , the bootstrap technique with resampling was used.^{10,11} For this analysis, additional data sets were compiled by repeated resampling from the original data set. We took this approach because there are no good formula-based methods to estimate confidence limits for variables calculated from three parameters (P1, P2, and P3), all of which vary interdependently.

With the resampling technique, the original dataset of results from the 80 subjects forms the source for samples to generate additional datasets. With this technique, random samples of individual results are repeatedly taken from the original dataset. When each sample is taken it is added to the new dataset, and when this has been repeated 80 times the new dataset has 80 results and is complete. Each time a sample is taken from the original dataset, it is replaced before the next random sample is taken. Consequently, the original dataset remains intact throughout, and the new dataset does not replicate the original but comprises a random sampling of the original results. This whole process is repeated to generate 99 additional datasets, all different but all derived from the

§ Simons J: Resampling: The "new statistics." <http://www.resample.com/textinfo.html>

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Table 2. Demographic Data

Dose (mg · kg ⁻¹)	Weight (kg)	Age (yr)	Gender (M/F)
0.0	73.4 ± 16.6	39.3 ± 11.8	15/5
0.4	75.0 ± 16.9	39.7 ± 7.5	18/2
0.8	78.6 ± 15.8	39.5 ± 14.3	14/6
1.2	67.4 ± 14.8	39.2 ± 10.5	10/10

Data are mean ± SD.

original set of results. These additional datasets were subjected to analysis by logistic regression, as described for the original dataset. The confidence limits for estimates of D₅₀, D₉₀, and D₉₅ are presented as the 5th and 95th percentiles of the results from the original plus 99 additional datasets.

To confirm that 100 datasets were sufficient, the confidence limits for D₅₀, D₉₀, and D₉₅ were calculated for 20, 40, 60, 80, and 100 datasets, and the results were examined.

Estimates of time until the reappearance of first response to TOF stimulation after the ED₉₀ and ED₉₅ doses of rocuronium were derived by linear regression.

Results

The four study groups did not differ with respect to age, weight, or gender distribution (table 2).

The fraction of successful intubations achieved with each dose of rocuronium is depicted in figure 1. There were six cases of failed intubation in the saline solution

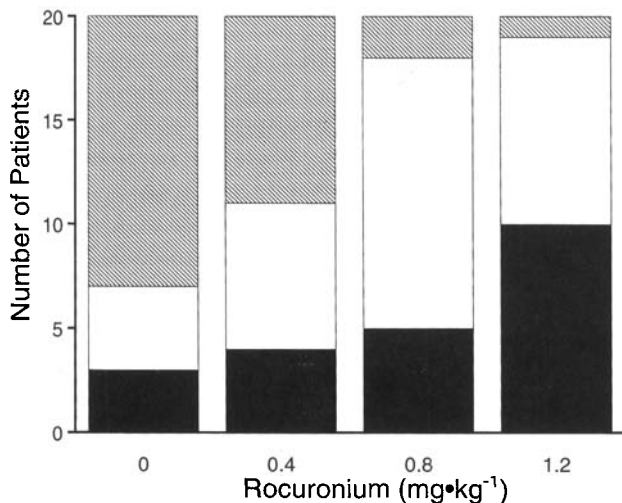


Fig. 1. Intubating conditions at each rocuronium dose. Black column = perfect conditions; white column = acceptable conditions; hatched column = unacceptable conditions.

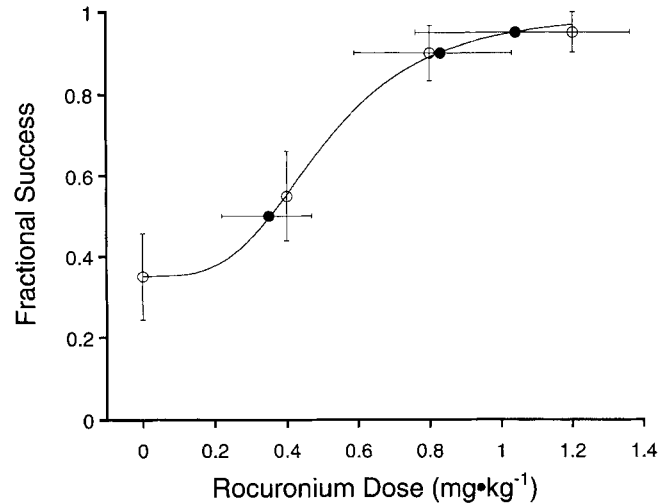


Fig. 2. Probability curve for successful rapid tracheal intubation with rocuronium generated from the model parameters derived from the original dataset (see fig. 1) by logistic regression. Fractional success in each rocuronium dose group is represented by the open circles (error bars are the SD). The calculated doses giving 50%, 90%, and 95% probability of successful intubation are filled circles, and the error bars are the 5th and 95th percentile range for these estimates.

control group and none in any of the groups receiving rocuronium. There were nine patients in the 0.4 mg/kg rocuronium group, two in the 0.8 mg/kg group, and one in the 1.2 mg/kg rocuronium group with an unacceptable intubation grade caused by sustained coughing with intubation. If intubation failed on the first attempt, it was always successfully performed on the second attempt after administration of additional propofol or rocuronium.

Estimates for D₅₀, D₉₀, and D₉₅ derived from the original dataset are 0.35, 0.83, and 1.04 mg/kg, respectively. The confidence intervals for D₅₀, D₉₀, and D₉₅ expressed as the 5th and 95th percentiles of the results from the original plus the 99 bootstrap datasets are 0.22-0.47, 0.59-1.03, and 0.76-1.36 mg/kg, respectively. The dose-response curve generated from the original data set is shown as figure 2. Confidence limits derived from increasing numbers of datasets are given in table 3.

In 79 patients, all four TOF responses were felt at completion of the initial intubation attempt, and in the remaining patient three responses were felt. The relationship between rocuronium dose and duration of action is demonstrated in figure 3. Patients from the saline solution control group were not included in the regression analysis. In three patients the duration of action was not recorded, in one because of equipment failure and in two because of lack of access to the patients' hands. The

Table 3. Confidence Intervals: Effect of Size of Dataset

Variable (best estimate)	Percentile	Number of Datasets				
		20	40	60	80	100
D50 (0.35 mg · kg ⁻¹)	5	0.25	0.16	0.16	0.21	0.22
	95	0.44	0.46	0.46	0.46	0.47
D90 (0.83 mg · kg ⁻¹)	5	0.59	0.56	0.59	0.59	0.59
	95	0.87	1.07	1.03	1.07	1.03
D95 (1.02 mg · kg ⁻¹)	5	0.75	0.74	0.76	0.76	0.76
	95	1.13	1.42	1.35	1.41	1.36

calculated durations of action of the D₉₀ and D₉₅ doses were 32 min and 46 min, respectively.

Discussion

The present investigation was in essence a dose-response study, with the response being the fraction of patients in whom rapid tracheal intubation was achieved successfully. With this approach, we were able to predict the dose required for a given probability of successful intubation. This study differs from previous investigations of rapid tracheal intubation facilitated by rocuronium using traditional methods because none of them attempted to define a dose-response relationship.^{2-7,12,13} In those previous studies, the incidence of successful intubation at different doses of rocuronium

(ranging for 0.6 to 1.2 mg/kg) was reported, but a probability of success was never defined.

Defining a dose of a drug in terms of probability of therapeutic success has several advantages over the more traditional approaches. First, it allows clinical decision making about choice of dose, which can incorporate weighing the consequences of that choice. With the approach used in this study, the importance of having a high probability of successful intubation can be weighed against the consequence, which is longer duration of action.

Second, use of our approach allows rapid determination of drug doses required to achieve specific therapeutic goals. The D₉₅ dose of rocuronium that we defined (1.04 mg/kg) is similar to the doses, 0.9–1.0 mg/kg, which have already been recommended in other studies.^{12,13} However, the process of determining that doses on the order of 1.0 mg/kg are necessary to facilitate rapid tracheal intubation has been one of evolution, over a period of years, incorporating the results from several different studies.^{2-7,12,13} Using the approach described in this study, the dose necessary to facilitate rapid tracheal intubation with a new neuromuscular blocking drug such as rapacuronium could be defined in a short period of time with one study.

Third, using probability allows for true comparative studies of drugs or factors influencing their action. For example, doses of different drugs that are truly equipotent for a given response can be determined. If the dose of succinylcholine that provides 95% probability of successful intubation was defined, then this would be the dose that was truly equipotent with the D₉₅ (1.04 mg/kg) of rocuronium. In a similar manner, the influence of different anesthetic regimens on the efficacy of rocuronium could be studied. For example, the question of whether different anesthetic induction drugs alter the D₉₅ dose could be asked and easily answered.

The technique we describe is not limited only to the study of rapid tracheal intubation with rocuronium. The

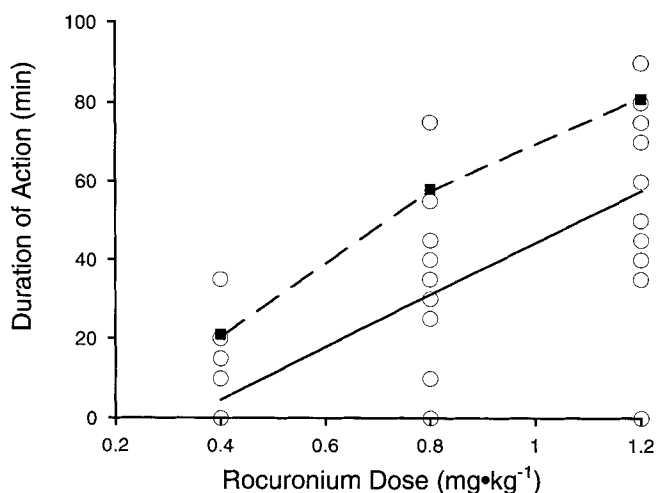


Fig. 3. Rocuronium dose plotted against duration of action (open circles). The line is the regression of duration versus dose (duration of action = 65.8 · dose - 21.3; $r^2 = 0.64$; $P < 0.005$). There are fewer than 20 circles in each group because of overlapping values. The filled boxes are the 95th percentile estimates for the duration of each dose, and the broken line simply connects these points.

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“response” can be any clearly defined clinical outcome; for example, we can find the dose of a drug that gives 95% probability of recovery within 30 min. In this case the response would be the fraction of patients recovering from the drug within 30 min. The drug studied could be any of the drugs used in anesthesia, as long as they have an effect (response) that can be measured.

The other significant difference between this and previous studies is that we used the technique of resampling with replacement to determine confidence limits for our estimates.^{10,11} By resampling from our original dataset, we created 99 additional dose–response datasets from the overall population represented by the original dataset. As a result, we were able to derive confidence limits for our estimates of the D_{90} and D_{95} doses. Thus, although our best estimate of D_{95} is 1.04 mg/kg, if successful rapid tracheal intubation is of critical importance, the clinician might feel more secure in using a dose of 1.36 mg/kg, which represents the 95th percentile for the upper range of this estimate. This larger dose is outside the range we studied and is greater than the maximum (1.2 mg/kg) recommended in the package insert. However, we predict that a dose of 1.36 mg/kg should have a duration of action of approximately 68 min and will have minimal risk of significant adverse cardiovascular effects.¹⁴ Studies using the more traditional approach of reporting only an incidence of success with a given dose cannot address the issue of confidence limits.

Increased probability of successful intubation using larger rocuronium doses carries with it the consequence of a longer duration of action. Figure 3 illustrates the relationship we found between rocuronium dose and duration of action. We defined duration of action as the time to return of the first TOF response, as this is the criterion most accessible to the clinician and represents the earliest point at which induced reversal with an anticholinesterase is appropriate. Our results show that a D_{90} dose of rocuronium (0.83 mg/kg) has a mean estimated duration of 32 min, with the 95th percentile for this estimate approximately 58 min. In comparison, a D_{95} dose of rocuronium (1.04 mg/kg) has a mean estimated duration of 46 min, with the 95th percentile for this estimate being almost 70 min. Thus, in an individual patient, the possibility of long duration of action must be balanced against the need for rapid tracheal intubation.

Figure 3 illustrates the approximate magnitude of prolongation of neuromuscular block with increasing doses of rocuronium. However, because the duration of action of rocuronium is dependent on the type and dose of drugs (particularly volatile agents) used to maintain an-

esthesia, figure 3 should not be interpreted as accurately predicting duration of action in conditions other than those in this study.

Conditions for tracheal intubation are significantly influenced by the drugs used to induce anesthesia. Adjustment of opioid dose^{7,15} or the use of increased doses of propofol or etomidate^{16,17} may permit a high probability of successful tracheal intubation with smaller doses of rocuronium than suggested by our results. In contrast, the use of thiopental for anesthetic induction may require use of larger doses than we describe.^{16,17} The “priming” and “timing” principles have been used to enhance intubation conditions with rocuronium,^{18–21} but these techniques carry the risks of premature weakness,¹⁸ pain on injection,²² and precipitation in the intravenous tubing.²³ Finally, succinylcholine may be considered a more appropriate drug, as it allows rapid tracheal intubation with short duration of action.^{2,13} None of these other techniques have been studied with probability of success as an endpoint, so detailed comparisons are not possible.

We found that successful rapid intubation is possible if no rocuronium is used. This result is agreement with previous studies showing good intubation conditions without neuromuscular block if an opioid is used as a part of the induction sequence.^{15,16} However, we determined that the probability of success without using rocuronium is only 35%, and this is unacceptably low in clinical situations in which rapid tracheal intubation is required.

All but one patient had four tactile TOF responses at the adductor pollicis muscle at the time of intubation, regardless of the intubating conditions. This finding is consistent with pharmacodynamic studies of rocuronium demonstrating a faster onset of neuromuscular block at the laryngeal muscles compared to the adductor pollicis.²⁴ This result further emphasizes that TOF responses at the adductor pollicis are not useful if one is attempting rapid tracheal intubation with rocuronium.

In this study we aimed to achieve tracheal intubation at 60 s after rocuronium injection. We chose 60 s because this is within the time range (60–90 s) recommended for rapid tracheal intubation,²⁵ and the range (45–75s) used in previous studies.^{5,7,12,13} We did not use cricoid pressure in our study, and in this way our technique differs from rapid sequence intubation for prevention of pulmonary aspiration of gastric contents. Cricoid pressure improves the view of the larynx during laryngoscopy, and it is possible that our intubating conditions could have been enhanced by the use of cricoid pres-

sure. However, we do not believe that the absence of cricoid pressure significantly influenced our results. In the patients in whom intubation was judged unacceptable it was not because of poor visualization of the larynx, but rather because we could not open the patient's mouth, the vocal cords remained closed during attempted intubation, or there was sustained coughing after placement of the endotracheal tube. Cricoid pressure would not have changed the outcome in these situations.

In conclusion, we determined doses of rocuronium that would give a high probability (90% and 95%) of facilitating successful rapid tracheal intubation and estimated the likely duration of action of these doses. In addition, we used resampling with replacement from our original data sample to derive confidence limits for these dose estimates. We believe these results provide information useful in the process of choosing an appropriate dose of rocuronium to facilitate rapid tracheal intubation, and that the techniques described can be applied to answer many other experimental questions.

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