Rapid Tracheal Intubation with Large-Dose Rocuronium: A Probability-Based Approach

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There are situations in anesthesia in which it may be desirable to achieve rapid tracheal intubation with perfect conditions, i.e., no coughing or straining. To determine the dose of rocuronium that gives a high probability of achieving perfect conditions for rapid (within 60 s) tracheal intubation, we administered a range of doses of rocuronium, some larger than used previously. Sixty adults, anesthetized with thiopental 4 mg/kg IV and alfentanil 10 μg/kg IV, received rocuronium 0.4 to 2.0 mg/kg IV. We used logistic regression to define the relationship of rocuronium dose to probability of achieving perfect intubation conditions. We estimated the doses giving 90% and 95% probability of achieving perfect intubation and used resampling to determine confidence limits for these estimates. Rocuronium 1.85 and 2.33 mg/kg gave, respectively, 90% and 95% probability of perfect intubation conditions. The confidence limits (5th and 95th percentile) for these estimates were 1.15 to 2.31 and 1.23 to 3.22 mg/kg, respectively. In conclusion, it is possible to achieve perfect intubation conditions with large doses of rocuronium, but the long duration of action and expense may limit the usefulness of the technique. **Implications:** We found that it is possible to have a 90% probability of achieving perfect conditions for rapid tracheal intubation with large (up to 2.0 mg/kg) doses of rocuronium. These large doses of rocuronium may be useful in, for instance, head trauma or open globe injuries if succinylcholine is contraindicated.

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Succinylcholine, the drug traditionally used to facilitate rapid tracheal intubation has, in many situations, been replaced by rocuronium (1–5). Rocuronium, in doses of 0.6–1.2 mg/kg IV, has proven to be as effective as succinylcholine 1.0 mg/kg IV in producing acceptable (good or excellent) conditions for rapid tracheal intubation (1–5). However, succinylcholine and rocuronium differ in their ability to provide excellent intubation conditions, with succinylcholine being superior in this respect (3,5).

A possible approach to improve the ability of rocuronium to produce perfect conditions for rapid tracheal intubation would be to increase the dose administered. We used doses of rocuronium (up to 2.0 mg/kg) larger than those previously investigated. In addition, we used a probability-based approach (6), to define the doses of rocuronium that would give a 90% and 95% probability of producing perfect conditions for rapid tracheal intubation.

Methods

After approval from our local institutional review board, written, informed consent was obtained from all patients. We studied 60 (ASA physical status I or II) adults admitted for elective surgical procedures. Patients aged more than 55 yr or less than 18 yr, having gastroesophageal reflux, weighing more than 30% above ideal body weight, suffering from neuromuscular disease, or undergoing treatment with drugs known to interfere with neuromuscular transmission were excluded. All patients enrolled had a Mallampati class 1 or 2 airway anatomy and no anticipated difficulty with mask ventilation or tracheal intubation.

Patients were premedicated with midazolam 0.01 mg/kg IV, within 15 min before the induction of anesthesia. In the operating room, routine monitoring of blood pressure, electrocardiogram and pulse oximetry was initiated. After preoxygenation with 100% oxygen for 3 min, alfentanil 10 μg/kg IV, thiopental 4 mg/kg IV, and a randomized, blinded dose of rocuronium were administered in rapid succession. The doses of rocuronium, 0.4, 0.8, 1.2, 1.6, or 2.0 mg/kg IV, were

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diluted in normal saline to a total volume of 20 mL in all cases. At 40 s after the injection of rocuronium, laryngoscopy was performed, with the goal of having 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 placed successfully within 30 s (i.e., 70 s after rocuronium administration), the attempt was recorded as a failure. All intubations were performed by one of the two authors, and the intubating conditions were graded according to the criteria outlined in Table 1 (7). Excellent scores in all 5 categories in Table 1 were required for a grading of perfect intubation; all other scores were considered failures. The investigator performing the intubation and assessing the conditions was blinded to the dose of rocuronium administered.

Before the induction of anesthesia, surface electrodes were placed over the ulnar nerve at the wrist. When the patient lost consciousness, train-of-four (TOF) stimulation (2 Hz for 2 s every 12 s) commenced. Immediately after tracheal intubation and every 5 min thereafter, the number of tactile responses to TOF stimulation was recorded. The duration of action of rocuronium was the time from injection until the return of the first tactile TOF response (7).

After tracheal intubation, anesthesia was maintained with isoflurane, 0.5%–1.0% or desflurane 3%–6% (end-tidal concentration) and fentanyl bolus doses as required. These doses of desflurane and isoflurane have similar effects on the dose-response relationship and time course of action of rocuronium (8,9). Mechanical ventilation was adjusted to maintain the end-tidal carbon dioxide partial pressure at 30–35 mm Hg. The patient's body temperature was kept above 36°C by forced-air warming.

The patient's heart rate and blood pressure were recorded before the induction of anesthesia and every minute for 5 min after tracheal intubation.

Logistic regression was used to analyze the dose-response curve (10), the response being the fraction of patients with perfect intubation conditions at each dose of rocuronium. This is an approach that we have used previously (6). The equation used for the logistic regression was

$$\text{fraction of success} = P3 + (1 - P3)(A/(A + 1))$$

where A is EXP(P1 + P2(logdose)). P1 and P2 are the inbuilt variables of the logistic regression program, and P3 is an additional variable, which allows for the proportion of patients who would have had successful intubation if no rocuronium were used. The doses of rocuronium that gave a 50%, 90%, and 95% probability of successful intubation (D50, D90 and D95, respectively) were calculated.

To obtain confidence limits for the estimates of the D50, D90, and D95, the bootstrap technique with resampling was used. The original data set was assumed to represent the very large population from which it was derived, and additional data sets were compiled by repeated resampling from the original data set (11–13). This approach was taken because there are no good formula-based methods to estimate confidence limits for variables calculated from 3 parameters (i.e., P1, P2, and P3) all of which vary, but are interdependent.

The original dataset comprised the intubation grade (i.e., perfect or not) of the 60 subjects and formed the source for samples to generate additional datasets. Generating a new dataset was started by randomly taking an individual result from the original dataset, and placing it in the new dataset. The original dataset was then reconstituted by replacing the sample that was taken, and thus, it remained intact throughout. This process was repeated until there were a total of 60 randomly sampled results in the new dataset. The new dataset did not replicate the original but was a random sampling of the original results.

This process was repeated to generate a total of 99 new datasets, all different, but all derived from the original set of results. Each of these new datasets was subjected to analysis by logistic regression, as described for the original dataset and generated an additional 99 values for D50, D90, and D95. 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 new datasets. To confirm that 100 datasets were sufficient, the confidence limits for the estimates of D50, D90, and D95 were derived for 20, 40, 60, 80, and 100 datasets, and the results were examined.

The relationships between the rocuronium dose and the duration of rocuronium-induced block was analyzed by least-squares linear regression analysis.

Patient physical characteristics in the five study groups were compared by analysis of variance or χ^2 as appropriate. For the 5 min after the rocuronium administration, the maximal changes in systolic blood pressure and heart rate from the preinduction level were measured, and compared among the different dose groups by using analysis of variance. In each rocuronium dose group, the frequency of >20% increase in cardiovascular responses (systolic blood pressure and heart rate) after the rocuronium administration was recorded, and intergroup differences tested by using χ^2 analysis.

A P-value < 0.05 was considered statistically significant.

Results

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

Table 1. Grading Criteria for Intubation Conditions

Criterion	Excellent	Good	Poor
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

Intubation conditions at each dose of rocuronium are shown in Figure 1. All patients were intubated within 60 s. The reason for less than perfect conditions in 3 patients in the 1.6-mg/kg group was movement of the diaphragm in response to intubation. The best estimates of D50, D90, D95, and the effect of number of datasets on resampling estimates of confidence limits are detailed in Table 3. The D50, D90, and D95 rocuronium doses were 0.89 mg/kg, 1.85 mg/kg, and 2.38 mg/kg, respectively (Table 3). The dose-response curve generated from the original dataset is shown in Figure 2.

Table 4 shows the number of tactile TOF responses observed at the time of tracheal intubation and the duration of the period of no tactile TOF response in each rocuronium dose group. The period of no tactile TOF response increased significantly with the dose of rocuronium ($P < 0.005$, $r^2 = 0.85$). The median duration of rocuronium 2.0 mg/kg was 110 min (range 80–160 min). The duration of no TOF response was not recorded in three patients, in one because of equipment failure and in two because of lack of access to the patients' hands.

The cardiovascular responses in each rocuronium dose group are shown in Table 4. In 68% of the patients, either systolic blood pressure or heart rate increased >20%, but this effect was not dose-related. The maximal change in cardiovascular response (systolic blood pressure or heart rate) did not differ among dosage groups.

Table 2. Patient Physical Characteristics

Dose group (mg/kg)	Weight (kg)	Age (yr)	Sex (M/F)
0.4	75 ± 18	42 ± 8	4/8
0.8	81 ± 9	43 ± 9	9/3
1.2	74 ± 16	39 ± 11	6/6
1.6	71 ± 13	40 ± 9	7/5
2.0	75 ± 12	33 ± 10	6/6

Data are mean ± SD or proportion.

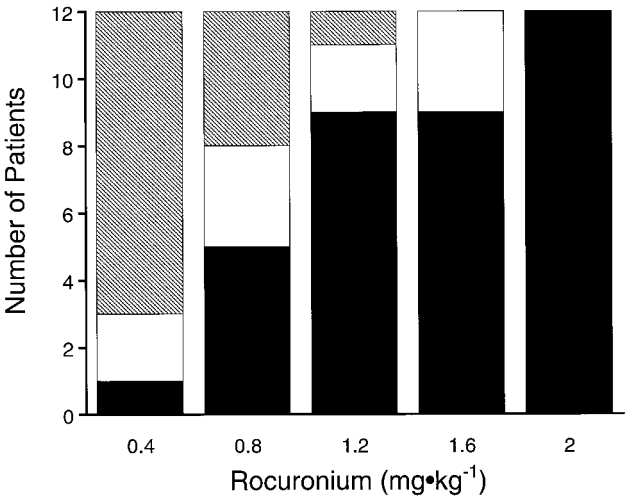

Figure 1. Intubating conditions at each rocuronium dose. Black column-excellent conditions, white column = good conditions, hatched column = poor conditions.

Discussion

Our goal in this study was to define doses of rocuronium that would provide a high probability of producing perfect conditions for tracheal intubation in patients in whom succinylcholine was relatively contraindicated. An example of such a group of patents is trauma victims with a severe head injury (14). In these patients, succinylcholine may be contraindicated because it can significantly increase intracranial pressure and serum potassium (15,16). Rocuronium, in contrast, does not increase intracranial pressure (17), and because of its nondepolarizing mechanism of action, it will not increase serum potassium concentration. We have found that rocuronium, in a dose of 2.0 mg/kg, can produce a greater than 90% probability of achieving perfect conditions for rapid tracheal intubation. The use of such a large dose of rocuronium should be balanced against the consequences.

Large doses will produce prolonged neuromuscular block. The median period of no tactile TOF response after rocuronium 2.0 mg/kg was approximately two hours. Such a long duration makes the large-dose rocuronium technique unsuitable in cases with short surgery time. However, if large doses are used in patients who will require prolonged tracheal intubation, such as those with head trauma, then prolonged block is not necessarily a disadvantage. We studied only patients whose physical examination suggested that airway management would be straightforward. We would of course caution against the use of large doses of rocuronium in patients for whom difficulty in airway management was anticipated, as prolonged neuromuscular block could compromise patient safety if an airway could not be secured.

Table 3. Best Estimates of Intubation Doses and Effect of Number of Datasets on Calculation of Confidence Intervals (5th and 95th percentiles)

Variable	Best estimate (mg/kg)	Percentile	Number of datasets				
			20	40	60	80	100
D50	0.89	5th	0.71	0.69	0.69	0.69	0.69
		95th	1.23	1.22	1.21	1.17	1.17
D90	1.85	5th	1.22	1.18	1.15	1.08	1.15
		95th	2.33	2.23	2.31	2.27	2.31
D95	2.38	5th	1.47	1.23	1.32	1.23	1.23
		95th	3.00	2.95	3.13	3.13	3.22

D50, D90, and D95 are the rocuronium doses giving, respectively, 50%, 90%, and 95% probability of perfect intubation conditions.

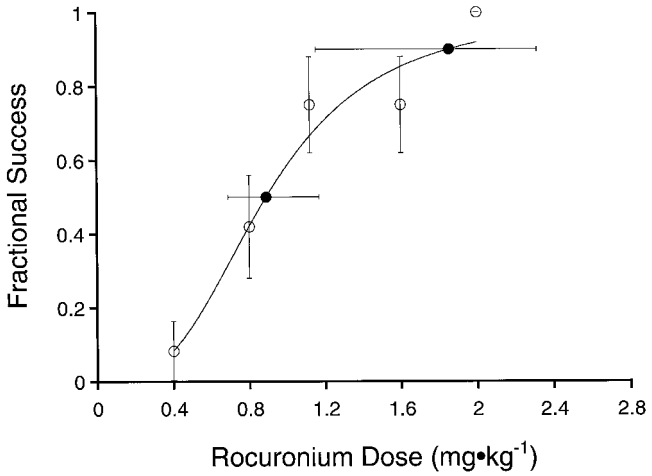

Figure 2. Probability curve for rapid tracheal intubation with rocuronium generated from the model variables derived from the original dataset (see Fig. 1) by logistic regression. Fractional success in achieving perfect conditions (all categories graded excellent) in each rocuronium dose group is represented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

Table 4. Neuromuscular and Cardiovascular Responses

Dose (mg/kg)	Neuromuscular responses		Maximal cardiovascular change (%)	
	TOF count (*n*)	Duration (min)	Systolic BP (mm Hg)	Heart rate (bpm)
0.4	4 (4–4)	0 (0–22)	30 (0–68)	7 (0–52)
0.8	4 (2–4)	30 (10–50)	24 (2–63)	8 (0–14)
1.2	4 (0–4)	60 (34–105)	29 (0–69)	7 (0–27)
1.6	3 (0–4)	76 (55–97)[a]	22 (0–67)	7 (0–47)
2.0	0 (0–4)	110 (80–160)[b]	17 (0–40)	5 (0–27)

Data presented as median values (range).
Duration = time from rocuronium injection until return of first tactile train-of-four response, TOF count = tactile train-of-four responses at intubation, BP = blood pressure.
[a] $n = 10$.
[b] $n = 11$.

The use of large doses of rocuronium also raises the issue of cost. An average 70-kg patient would require almost 140 mg of rocuronium to produce a high probability of perfect intubation conditions. At our institution (University of California, San Francisco), this dose would involve a drug acquisition cost of approximately $50. This cost can be justified if obtaining perfect intubation conditions is a clinical priority and helps prevent an adverse patient outcome.

Our best estimate for the D95 was 2.38 mg/kg, i.e., outside the range of doses we administered. Consequently, this may not be a reliable estimate. A possible reason why we obtained this high estimate for D95 is that we had very stringent criteria for what constituted perfect intubation conditions. In particular, we considered any movement of the diaphragm in response to intubation a failure. Three patients in the 1.6-mg/kg dose group had only a slight diaphragmatic response to intubation, and the intubations were, therefore, deemed failures. It is likely that if our criteria had been less stringent, some or all of these three patients would have been judged to have had perfect conditions, and the estimate for D95 might have fallen within the range of doses we administered.

Because we envisioned our results as having relevance to head trauma patients and because such injury is often associated with injury to other organs and, hence, hemodynamic instability, we chose to administer only moderate doses of thiopental (4 mg/kg) and alfentanil (10 μg/kg)—doses that clinicians might feel comfortable with in an emergency situation. We chose alfentanil as a supplement to thiopental for the induction of anesthesia for two reasons. First, the use of an opioid improves the quality of intubating conditions (4,18). Second, we wanted an opioid that we could administer at the induction of anesthesia and that would be effective at the time of intubation; alfentanil has an appropriately rapid onset to achieve this (19).

It would be possible to achieve perfect intubation conditions with smaller doses of rocuronium if we had used larger doses of induction drugs (4,18) or had used propofol instead of thiopental (20,21). However, because we envisioned trauma victims as a group to which our results might have relevance, we wanted to

use a "light" general anesthetic and to avoid techniques associated with greater risk of hypotension (22,23). Thus, we were relying more on the effect of rocuronium and less on the central depression from anesthesia to facilitate intubation.

Another mechanism to improve the probability of achieving perfect conditions would be to delay the time of intubation from 60 to 90 seconds after the rocuronium administration. There is no clear consensus on the time interval that constitutes rapid tracheal intubation. In most recent studies, laryngoscopy has commenced between 45 and 60 seconds after the rocuronium administration. The priority attached to the rapidity of tracheal intubation is a clinical decision, individualized to each situation. We hope that our results will add to the information available to the clinician and aid in their decision-making process.

We found that patient readiness for intubation could not be judged by the tactile TOF responses, because intubation conditions were perfect in 5 of 12 patients in the 2.0-mg/kg group, who still had responses at the time of intubation. This observation is consistent with the finding that the onset time of rocuronium is faster at the laryngeal muscles than at the adductor pollicis (24).

To date, there are no published studies of the cardiovascular effects of rocuronium in doses of 1.6 or 2.0 mg/kg. We observed no dose-related changes in heart rate and blood pressure. This is consistent with an earlier study in which doses up to 1.2 mg/kg were not associated with significant cardiovascular effects (25). We believe that, with the technique of rapid tracheal intubation we used, any cardiovascular effects of rocuronium were masked by the concurrent response to laryngoscopy and intubation.

In conclusion, it is possible to have a high probability of achieving perfect conditions for rapid tracheal intubation with rocuronium and "light" general anesthetic. However, this approach involves a long duration of neuromuscular block and significant drug cost. The technique of using a large dose of rocuronium to achieve perfect conditions for tracheal intubation may have application in situations in which succinylcholine is relatively contraindicated.

References

1. Andrews JI, Kumar N, van den Brom RH, et al. A large simple randomized trial of rocuronium versus succinylcholine in rapid-sequence induction of anaesthesia along with propofol. Acta Anaesthesiol Scand 1999;43:4–8.
2. Fuchs-Buder T, Sparr HJ, Ziegenfub T. Thiopental or etomidate for rapid sequence induction with rocuronium? Br J Anaesth 1998;80:504–6.
3. McCourt KC, Salmela L, Mirakhur RK, et al. Comparison of rocuronium and suxamethonium for use during rapid sequence induction of anaesthesia. Anaesthesia 1998;53:867–71.
4. Sparr HJ, Giesinger S, Ulmer H, et al. Influence of induction technique on intubating conditions after rocuronium in adults: comparison with rapid-sequence induction using thiopentone and suxamethonium. Br J Anaesth 1996;77:339–42.
5. Sparr HJ, Luger TJ, Heidegger T, Putensen-Himmer G. Comparison of intubating conditions after rocuronium and suxamethonium following "rapid-sequence induction" with thiopentone in elective cases. Acta Anaesthesiol Scand 1996;40:425–30.
6. Kirkegaard-Nielsen H, Caldwell JE, Berry PD. Rapid tracheal intubation with rocuronium: a probability approach to determining dose. Anesthesiology 1999;91:131–6.
7. Viby-Mogensen J, Engbaek J, Eriksson LI, et al. Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents. Acta Anaesthesiol Scand 1996;40:59–74.
8. Kumar N, Mirakhur RK, Symington MJ, McCarthy GJ. Potency and time course of action of rocuronium during desflurane and isoflurane anaesthesia. Br J Anaesth 1996;77:488–91.
9. Wulf H, Kahl M, Ledowski T. Augmentation of the neuromuscular blocking effects of cisatracurium during desflurane, sevoflurane, isoflurane or total i.v. anaesthesia. Br J Anaesth 1998;80:308–12.
10. Engelman L. Stepwise logistic regression. In: Dixon WJ, ed. BMDP statistical software. Berkeley: University of California Press, 1990:1013–46.
11. Manly BFJ. The bootstrap. In: Manly BFJ, ed. Randomization, bootstrap and Monte Carlo methods in biology. London: Chapman and Hall, 1997:34–68.
12. Mossman D. Resampling techniques in the analysis of non-binormal ROC data. Med Decis Making 1995;15:358–66.
13. Simons J. The "new statistics." Available at http://www.resample.com/textinfo.html. Accessed March 23, 1999.
14. Silber SH. Rapid sequence intubation in adults with elevated intracranial pressure: a survey of emergency medicine residency programs. Am J Emerg Med 1997;15:263–7.
15. Miller RD, Savarese JJ, Lien CA, Caldwell JE. Pharmacology of muscle relaxants and their antagonists. In: Miller RD, ed. Anesthesia. New York: Churchill Livingstone, 1994:417–87.
16. Frankville DD, Drummond JC. Hyperkalemia after succinylcholine administration in a patient with closed head injury without paresis. Anesthesiology 1987;67:264–6.
17. Schramm WM, Strasser K, Bartunek A, et al. Effects of rocuronium and vecuronium on intracranial pressure, mean arterial pressure and heart rate in neurosurgical patients. Br J Anaesth 1996;77:607–11.
18. Scheller MS, Zornow MH, Saidman LJ. Tracheal intubation without the use of muscle relaxants: a technique using propofol and varying doses of alfentanil. Anesth Analg 1992;75:788–93.
19. Scott JC, Ponganis KV, Stanski DR. EEG quantitation of narcotic effect: the comparative pharmacodynamics of fentanyl and alfentanil. Anesthesiology 1985;62:234–41.
20. Stevens JB, Vescovo MV, Harris KC, et al. Tracheal intubation using alfentanil and no muscle relaxant: is the choice of hypnotic important? Anesth Analg 1997;84:1222–6.
21. McKeating K, Bali IM, Dundee JW. The effects of thiopentone and propofol on upper airway integrity. Anaesthesia 1988;43:638–40.
22. Beck GN, Masterson GR, Richards J, Bunting P. Comparison of intubation following propofol and alfentanil with intubation following thiopentone and suxamethonium. Anaesthesia 1993;48:876–80.
23. Grounds RM, Twigley AJ, Carli F, et al. The haemodynamic effects of intravenous induction: comparison of the effects of thiopentone and propofol. Anaesthesia 1985;40:735–40.
24. Wright PMC, Caldwell JE, Miller RD. Onset and duration of rocuronium and succinylcholine at the adductor pollicis and laryngeal adductor muscles in anesthetized humans. Anesthesiology 1994;81:1110–5.
25. Levy JH, Davis GK, Duggan J, Szlam F. Determination of the hemodynamics and histamine release of rocuronium (Org 9426) when administered in increased doses under N_2O/O_2-sufentanil anesthesia. Anesth Analg 1994;78:318–21.