

## Onset and Duration of Rocuronium and Succinylcholine at the Adductor Pollicis and Laryngeal Adductor Muscles in Anesthetized Humans

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**Background:** Rocuronium, a new nondepolarizing muscle relaxant, has a rapid onset of activity and may be suitable as a component of a rapid-sequence induction of anesthesia. We evaluated a range of doses on onset and duration of effect at the larynx and the adductor pollicis and compared these characteristics with those of succinylcholine.

**Methods:** Forty-eight patients aged 18–70 yr, of ASA physical status 1–3, were randomly allocated to receive succinylcholine (1 mg/kg) or one of three doses of rocuronium (0.4, 0.8, or 1.2 mg/kg) during surgery. Anesthesia was induced and maintained with propofol and fentanyl. The trachea was intubated without the use of muscle relaxants, and the cuff of the endotracheal tube placed between the vocal cords. Neuromuscular transmission was monitored by mechanomyography at the laryngeal adductor and adductor pollicis muscles. Muscular activity was evoked with supramaximal stimuli in a train-of-four sequence every 12 s to the anterior branch of the recurrent laryngeal nerve and the ulnar nerve.

**Results:** At the laryngeal adductors, peak effect exceeded 99% in all patients given succinylcholine and in none (0%), five (42%), and ten (83%) of those given rocuronium 0.4, 0.8, and 1.2 mg/kg, respectively. At the adductor pollicis, peak effect exceeded 99% in all study patients except two who received rocuronium 0.4 mg/kg (peak effects 91% and 97%). Onset of effect with succinylcholine was significantly more rapid at the laryngeal adductors ( $34 \pm 12$  s, mean  $\pm$  SD) than at the adductor pollicis ( $56 \pm 15$  s); this was true also for rocuronium 0.4 mg/kg ( $92 \pm 29$  s and  $155 \pm 40$  s for the laryngeal adductors and adductor pollicis, respectively). Onset times were similar at the two muscle groups with rocuronium 0.8 and 1.2 mg·kg<sup>-1</sup>:  $96 \pm 29$  and  $74 \pm 36$  s with 0.8 mg/kg and  $54 \pm 30$  and  $65 \pm 21$  s with 1.2 mg/kg at the laryngeal adductors and the adductor pollicis, respectively.

**Conclusions:** The laryngeal adductors are more resistant to the action of rocuronium than is the adductor pollicis. Consequently, the onset of effect of rocuronium, in doses greater than 0.8 mg/kg, is similar to that of succinylcholine at the adductor pollicis but is significantly delayed compared with that of succinylcholine at the laryngeal adductors. (Key words: Muscle, skeletal: laryngeal adductors. Neuromuscular relaxants: rocuronium; succinylcholine.)

ROCURONIUM is a new nondepolarizing muscle relaxant having a rapid onset of action demonstrated by the response of the adductor pollicis muscle to ulnar nerve stimulation.<sup>1</sup> It may therefore be suitable as a component of a rapid-sequence induction of anesthesia. However, the time course and potency of muscle relaxants differ at laryngeal muscles and the diaphragm as compared with the adductor pollicis.<sup>2,3</sup> One consequence of this may be that relaxation of laryngeal muscles might be less than complete when intubation is attempted rapidly after induction of anesthesia. The differing effects of rocuronium at the adductor pollicis and the laryngeal muscles have been described for small doses resulting in mostly submaximal effect,<sup>4</sup> but not with the larger doses that might be used with a rapid-sequence induction of anesthesia. Accordingly, the current study sought to establish both the magnitude and rate of onset of neuromuscular block at the adductor pollicis and laryngeal adductor muscles by rocuronium in doses likely to be used for tracheal intubation (0.4 mg/kg–1.2 mg/kg). These characteristics were compared with those of succinylcholine 1 mg/kg.

### Materials and Methods

After obtaining the approval of the institutional review board and written informed consent, we studied 48 patients aged 18–70 yr, ASA physical status 1–3, scheduled to undergo surgery  $\geq 2$  h duration. The sample size was determined to have an 80% chance of de-

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## ROCURONIUM AND SUCCINYLSCHOLINE ONSET

**Table 1. Age, Weight, Height, and Gender Distribution of the Subjects**

	Rocuronium			Succinylcholine
	0.4 mg/kg (n = 12)	0.8 mg/kg (n = 12)	1.2 mg/kg (n = 12)	1.0 mg/kg (n = 12)
Age (yr)	50 ± 16	45 ± 16	43 ± 15	41 ± 19
Weight (kg)	68 ± 14	75 ± 11	68 ± 15	67 ± 11
Height (cm)	167 ± 11	175 ± 8	171 ± 13	167 ± 9
Gender (M:F)	4:8	9:3	5:7	7:5

Values are mean ± SD. There were no significant differences between the groups.

etecting a 30 s difference in onset time (at the vocal cords) between any 2 groups, assuming a standard deviation in this measure of 22 s.<sup>4</sup> Patients who were obese, pregnant, had significant renal, hepatic, metabolic or neuromuscular disease, or who were receiving medication known to influence neuromuscular transmission were excluded. Approximately 1 h before the induction of anesthesia midazolam 0.02–0.08 mg/kg was given intravenously. Patients were then randomly allocated to receive rocuronium 0.4, 0.8, or 1.2 mg/kg or succinylcholine 1 mg/kg during their surgery.

Anesthesia was induced with fentanyl 1–4 µg/kg followed by propofol 1.5–3 mg/kg administered intravenously. One minute after propofol administration, laryngoscopy was performed and an endotracheal tube was placed in the trachea with its cuff lying between the vocal cords and filled with sufficient air to prevent an audible leak during application of positive pressure to the airway. Mechanical ventilation was initiated with oxygen in air, and end-tidal partial pressure of carbon dioxide was maintained at 35–40 mmHg. Anesthesia was maintained with propofol 80–160 µg · kg<sup>-1</sup> · min<sup>-1</sup> and intermittent boluses of fentanyl 25–200 µg. Nasopharyngeal temperature was maintained >35°C using forced-air warming. Vital signs were monitored according to current standards.

Neuromuscular transmission was monitored at both the adductor pollicis and the laryngeal adductor muscles. The ulnar nerve was stimulated using surface electrodes placed at the wrist. The anterior branches of both recurrent laryngeal nerves were stimulated using surface electrodes placed on the forehead (positive) and at the notch of the thyroid cartilage (negative).<sup>5</sup> With both muscle groups, supramaximal stimuli of 0.2 ms duration were delivered in a train-of-four sequence at 2 Hz every 12 s (Digistim II, Neurotechnology, Houston, TX). The evoked twitch tension of the ad-

ductor pollicis muscle was measured with a force transducer (Myotrace, Life-Tech, Houston, TX) while preload was maintained at 300–500g. The evoked force of vocal cord adduction was evaluated by quantification of the pressure changes in the inflatable cuff of the endotracheal tube with preload maintained constant at 10–30 cmH<sub>2</sub>O. Pressure changes were detected using a pressure transducer (P23 ID, Gould Electronics, Valley View, OH). Signals from the force and pressure transducers were amplified (DC Bridge amplifier, Gould) and recorded on a strip-chart recorder.

After stable recording of neuromuscular transmission had been established at both muscle groups for a minimum of 10 min, the amplitude of the first response (T1) in each train-of-four sequence was taken as the control to which all subsequent T1 were compared. Rocuronium 0.4, 0.8, or 1.2 mg/kg or succinylcholine 1 mg/kg as determined before surgery was injected over a 5-s period directly into a large forearm vein. After administration of rocuronium, neuromuscular transmission monitoring was continued until T1 had recovered to a minimum of 25% of control at both muscle groups; after succinylcholine, recording was continued until T1 recovery was complete.

The following variables were determined for each muscle group in each patient: time to first depression of T1 (lag time); time to maximum block or 12 s after last detectable twitch when 100% twitch depression occurred (onset time); the maximum T1 depression (peak effect); and the time until T1 recovered to 25% of its control value.

The effect of rocuronium dose on lag time, onset time, peak effect, and time to 25% recovery of T1 at both muscle groups was determined by analysis of variance. After log transformation of onset time at the adductor pollicis and the laryngeal adductors, onset and duration variables and peak effects were compared between the succinylcholine group and the three rocuronium groups using analysis of variance with Dunnett's test for comparison to control (succinylcholine). Within a drug group, comparisons between muscle groups were made using a paired-sample *t* test. Data are reported as individual values or as mean ± SD, and *P* < 0.05 identified statistically significant differences.

## Results

Each study group consisted of 12 patients; the groups were similar in age, weight, height, and gender distribution (table 1).

### Comparisons Between Drug Groups

**Adductor Pollicis.** Results for the adductor pollicis are summarized in table 2. Peak effect exceeded 99% in all patients studied, with the exception of two patients who received rocuronium 0.4 mg/kg (peak effects 91% and 97%). Onset time decreased significantly with increasing dose of rocuronium; at the greater doses (0.8 and 1.2 mg/kg), lag times and onset times were similar to those of succinylcholine. Succinylcholine lag and onset times were significantly shorter than those of rocuronium 0.4 mg/kg. Time to 25% recovery (clinical duration) increased significantly with increasing dose of rocuronium and was significantly longer with all doses of rocuronium than that for succinylcholine.

**Laryngeal Adductor Muscles.** Results for the laryngeal adductor muscles are summarized in table 3. Peak effect exceeded 99% in all patients given succinylcholine and in none (0%), five (42%), and ten (83%) of those who received rocuronium 0.4, 0.8 and 1.2 mg/kg, respectively (table 3). Lag time decreased significantly with increasing doses of rocuronium, but was significantly longer after rocuronium 0.4 mg/kg than after succinylcholine. Onset time also decreased significantly with increasing doses of rocuronium but remained significantly longer with all doses than onset for succinylcholine. Time to 25% recovery was significantly longer after 1.2 mg/kg rocuronium than after 0.8 mg/kg and significantly exceeded that for succinylcholine after these two doses; this variable could not be determined for the smallest dose of rocuronium.

### Comparisons Between Muscles

Onset of effect was significantly more rapid at the laryngeal adductor muscles than at the adductor pollicis (fig. 1) with succinylcholine and rocuronium 0.4 mg/kg but did not differ between muscle groups with rocuronium 0.8 mg/kg and 1.2 mg/kg. Time to 25% recovery was less at the larynx than at the adductor pollicis in all study groups except that given the smallest dose of rocuronium in whom this parameter could not be determined. The full recovery profile of succinylcholine at both muscles is illustrated in figure 2.

## Discussion

Consistent with previous studies,<sup>6</sup> we found that time to onset of effect of rocuronium 0.8 and 1.2 mg/kg at the adductor pollicis was similar to that of succinylcholine (table 2). In contrast, at the laryngeal adductor

muscles, onset was slower and more variable and peak effect less and more variable, with all doses of rocuronium than with succinylcholine. Peak effect differed at the two muscle groups with that of rocuronium reduced at the laryngeal adductors relative to the adductor pollicis. Succinylcholine 1 mg/kg produced complete block at both muscles, with onset consistently more rapid at the larynx than at the adductor pollicis.

A previous investigation of rocuronium found a more rapid onset of action at the larynx than at the adductor pollicis.<sup>4</sup> We observed such a relationship only after rocuronium 0.4 mg/kg. Both sets of observations can be explained by considering the relationship between dose and onset time at muscles with differing sensitivity. The rate of onset of neuromuscular block is defined by the time to maximum block for doses producing <99% block or time to complete abolition of a response, for doses producing >99% or complete block.<sup>7</sup> Onset time for an incomplete block is influenced primarily by the equilibration rate to the biophase and is not dose-dependent for rocuronium<sup>8</sup> (or other muscle relaxant drugs).<sup>3,9</sup> In contrast, onset time with a dose producing complete block is influenced primarily by the degree to which the administered dose exceeds that required for a complete block; onset time is therefore dose-dependent, with a minimum limit determined by the circulation time (because a large dose will reach effective concentrations in the biophase upon delivery by the circulation). The transition from onset resulting from biophase equilibration to that due to circulation time begins at the dose producing complete block; larger doses are therefore required to initiate this transition at muscles with reduced sensitivity to muscle relaxants (fig. 3). Hence, a dose that produces incomplete block at all targeted muscle groups should result in more rapid onset at the muscle where drug diffuses most rapidly from blood to the site of action, such as the larynx in the current study. We observed this effect with two patients who received rocuronium, 0.4 mg/kg, in whom peak effect at the larynx was more rapid than at the adductor pollicis. Similarly, a dose producing complete block at the adductor pollicis and incomplete block at the laryngeal adductors should increase the rate of onset at the adductor pollicis but not the larynx. Consistent with this, we observed similar onset times at the adductor pollicis and the larynx with rocuronium 0.8 and 1.2 mg/kg.

A previous study of succinylcholine has demonstrated more rapid onset of effect at the laryngeal adductors than the adductor pollicis after doses insufficient to

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**Table 2. Time Course of Action and Peak Effect Data at the Adductor Pollicis**

	Rocuronium			Succinylcholine 1.0 mg/kg (n = 12)
	0.4 mg/kg (n = 12)	0.8 mg/kg (n = 12)	1.2 mg/kg (n = 12)	
Lag time (s)	38 ± 8† (27-53)	33 ± 7 (24-46)	30 ± 11 (15-51)	25 ± 7 (14-38)
Onset time (s)*	155 ± 40† (96-216)	74 ± 36 (45-145)	65 ± 21 (35-100)	56 ± 15 (36-75)
Peak effect (%T1 depression)	99 ± 3 (91-100)	100 ± 0 (100-100)	100 ± 0 (100-100)	100 ± 0 (100-100)
Clinical duration (min)*	24 ± 7† (8-38)	44 ± 10† (26-54)	67 ± 25† (39-118)	8 ± 2 (5-12)

Values are mean ± SD (range in parentheses).

\*  $P < 0.05$  dose-related effect with rocuronium.

†  $P < 0.05$  versus succinylcholine.

result in complete block.<sup>9</sup> In the current study, the dose of succinylcholine was large enough to achieve complete block at both muscles in all cases. Onset of effect was invariably more rapid at the laryngeal adductors than at the adductor pollicis, with onset times tightly clustered around 32 and 56 s, respectively. Consistent with the discussion above, we speculate that these times may represent the lower limit of onset time determined by circulation time.

Onset of effect of rocuronium 1.2 mg/kg at the adductor pollicis in our patients was similar in magnitude and variability to that after succinylcholine 1 mg/kg (confirming the observations of Magorian *et al.*<sup>6</sup>) but slower at the larynx. Theoretically, this might produce

less favorable intubating conditions with rocuronium. However, several investigators have reported intubating conditions after rocuronium (in similar doses) to be similar to those seen after succinylcholine.<sup>6,10,11</sup> The reported quality of the intubating conditions in these studies may have been affected by the use of anesthetic techniques that obscured differences between the muscle relaxants. For example, the use of propofol or opioids during the induction of anesthesia may produce acceptable intubating conditions without the use of muscle relaxants.<sup>12-15</sup> In one study of intubating conditions, patients were premedicated intravenously with both fentanyl and midazolam,<sup>6</sup> and in another, anesthetized with propofol and alfentanil.<sup>11</sup> Our study de-

**Table 3. Time Course of Action and Peak Effect Data at the Laryngeal Adductors**

	Rocuronium			Succinylcholine 1.0 mg/kg (n = 12)
	0.4 mg/kg (n = 12)	0.8 mg/kg (n = 12)	1.2 mg/kg (n = 12)	
Lag time (s)*	36 ± 9† (24-56)	28 ± 6‡ (20-38)	25 ± 9‡ (13-41)	23 ± 6‡ (11-34)
Onset time (s)*	92 ± 29†‡ (47-135)	96 ± 45† (44-183)	54 ± 30† (24-134)	34 ± 12‡ (18-58)
Peak effect (%T1 depression)*	70 ± 15†‡ (43-93)	93 ± 7‡ (79-100)	99 ± 3 (88-100)	100 ± 0 (100-100)
Duration to T1 = 25% (min)*	NA	25 ± 15†‡§ (3-54)	43 ± 13†‡ (24-65)	4.3 ± 1.6‡ (2-8)

Values are mean ± SD (range in parentheses). NA = not applicable.

\*  $P < 0.01$  dose-related effect with rocuronium.

†  $P < 0.05$  versus succinylcholine.

‡  $P < 0.05$  versus value at the adductor pollicis.

§ n = 10.

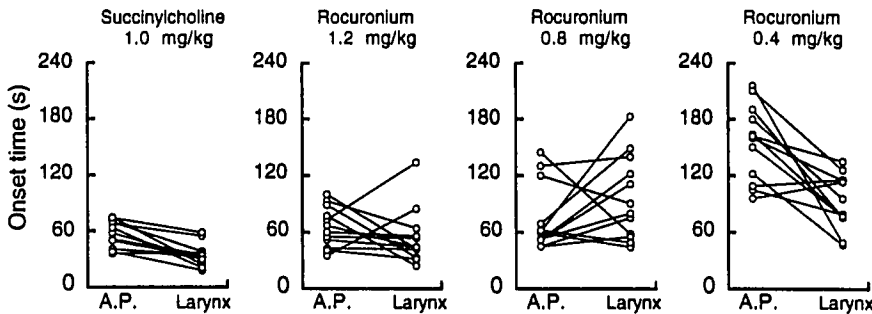


Fig. 1. Onset times for individual patients. A line joins values for each patient for the two muscles. After succinylcholine and rocuronium 1.2 mg/kg, onset at the adductor pollicis was similar for the two drugs; at the larynx it was faster after succinylcholine. With succinylcholine and rocuronium 0.4 mg/kg, onset time at the larynx was more rapid than at the adductor pollicis; with rocuronium 0.8 and 1.2 mg/kg, onset time was similar at the two muscle groups.

sign did not permit us to evaluate intubating conditions. However, intubating conditions in orally premedicated (temazepam) patients in whom anesthesia was induced with thiopental and small doses of fentanyl are reported to be less favorable with rocuronium 0.6 mg/kg than with succinylcholine 1 mg/kg 60 s after administration.<sup>16</sup>

Our study design permitted observation of the relative durations of action of the muscle relaxants at the two muscle groups. The measurement of effect at the larynx is subject to more variation and interference than mechanomyography at the adductor pollicis.<sup>5</sup> Nonetheless, we consistently observed that the duration of effect of rocuronium was 20–30 min less at the larynx than at the adductor pollicis. A shorter duration of effect has been noted at the larynx previously for both rocuronium<sup>4</sup> and other muscle relaxants,<sup>2,9</sup> and is attributed to the relative resistance of this group of muscles to neuromuscular blockade as compared with the adductor pollicis.<sup>2</sup> Similarly, we found a shortened duration of effect of succinylcholine at the larynx such

that recovery was almost complete in only 6–8 min after administration compared with 10–12 min at the adductor pollicis. The time course of action of subparalyzing doses of succinylcholine has been studied previously<sup>9</sup> but the very short duration of effect at the larynx of this standard intubating dose may be of significance to the clinician; the duration of complete relaxation of the laryngeal muscles is only one-half of that indicated by monitoring at the adductor pollicis.

To summarize, we observed, as expected, a relative resistance to the effect of rocuronium at the laryngeal adductor muscles compared with that at the adductor pollicis. Onset of neuromuscular block at the larynx was slower after rocuronium 0.4–1.2 mg/kg than after succinylcholine 1.0 mg/kg. Larger doses of rocuronium might shorten onset time at the larynx but also would

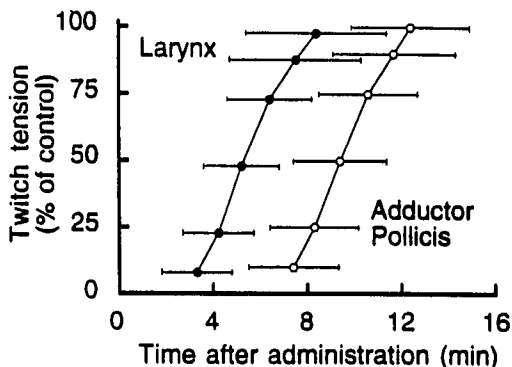


Fig. 2. Recovery profile after succinylcholine 1 mg/kg at the laryngeal adductors and at the adductor pollicis. Recovery of twitch tension (T1) was almost complete at the laryngeal adductors before any recovery occurred at the adductor pollicis.

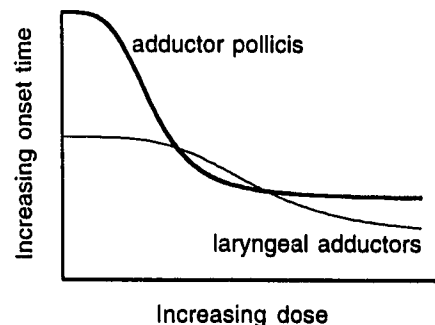


Fig. 3. Relation between onset time and dose of a muscle relaxant at the two muscles. With a small dose, which produced incomplete block, onset time was shorter at the larynx than at the adductor pollicis (for rocuronium approximately 180 s at the adductor pollicis and 100 s at the larynx [Meistelman *et al.*<sup>4</sup>]) and was not dose-related with either muscle. As dose increased and complete block occurred, onset time decreased until it reached a minimum, limited by circulatory parameters (speculatively 55 s at the adductor and 30 s at the larynx). As a result of the greater resistance of the larynx to neuromuscular block, the onset time decreased only at larger doses, and for some doses onset time was more rapid at the adductor pollicis.

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prolong duration. Rocuronium represents the most rapid onset nondepolarizing muscle relaxant drug currently available. However, truly to emulate the onset characteristics of succinylcholine, a drug must have an additional characteristic: it must, like succinylcholine, have a pharmacokinetic profile that allows the administration of very large doses without prolonging duration of action.

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