Rocuronium (ORG 9426) neuromuscular blockade at the adductor muscles of the larynx and adductor pollicis in humans

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The effects of rocuronium, 0.25 or 0.5 mg · kg^{-1}, were measured simultaneously on the adductor muscles of the larynx and adductor pollicis in 14 adult patients. Anaesthesia was induced and maintained with propofol and fentanyl. Tracheal intubation was performed without muscle relaxants. The recurrent laryngeal and ulnar nerves were both stimulated supramaximally, at the notch of the thyroid cartilage and at the wrist respectively, using train-of-four stimulation. The laryngeal response was evaluated by measuring the pressure change in the cuff of a tracheal tube positioned between the vocal cords. Onset time, intensity of blockade and duration of action were less at the larynx than at the adductor pollicis. After rocuronium, 0.25 mg · kg^{-1}, the onset time (interval between injection and maximal T_1 blockade) was 1.6 ± 0.1 min and 3.0 ± 0.3 min (mean ± SEM) at the laryngeal muscles and adductor pollicis, respectively ($P < 0.01$ between muscles). Maximum blockade was 37 ± 8% and 69 ± 8%, respectively ($P < 0.05$), and time to 90% T_1 recovery was 7 ± 1 min and 20 ± 4 min, respectively ($P < 0.05$). With 0.5 mg · kg^{-1}, the onset time was also more rapid at the vocal cords (1.4 ± 0.1 min) than at the adductor pollicis (2.4 ± 0.2 min, $P < 0.001$). Maximum blockade was 77 ± 5% and 98 ± 1%, respectively ($P < 0.01$), and time to 90% T_1 recovery was 22 ± 3 min and 37 ± 4 min, respectively ($P < 0.01$). It is concluded that with rocuronium onset and recovery are faster at the laryngeal adductor muscles, but blockade is less intense than at the adductor pollicis. These findings are similar to the observations made previously with vecuronium, except that rocuronium had a faster onset at both muscles.

Le but de cette étude était de mesurer chez 14 sujets adultes l'effet du rocuronium, 0,25 ou 0,5 mg · kg^{-1}, à la fois sur les muscles adducteurs du larynx et sur l'adducteur du pouce. L'induction et l'entretien de l'anesthésie se sont effectués à l'aide de propofol et de fentanyl. On n'a pas utilisé de curare pour l'intubation trachéale. On a appliqué une stimulation supramaximale en train-de-quatre à l'échancrure du cartilage thyroïde, pour le nerf récurrent laryngé, et au poignet, pour le nerf cubital. La contraction des muscles laryngés produisait un changement de pression dans le ballonnet de la sonde trachéale, placé entre les cordes vocales. Le temps d'installation, le bloc maximum et la durée d'action étaient moindres au niveau du larynx qu'à l'adducteur du pouce. Après injection de 0,25 mg · kg^{-1} de rocuronium, le temps d'installation (intervalle entre l'injection et bloc maximum de T_1) était de 1,6 ± 0,1 et de 3,0 ± 0,3 min (moyenne ± écart type de la moyenne) pour les muscles laryngés et l'adducteur du pouce, respectivement ($P < 0,01$ entre les muscles). Le bloc maximum se situait à 37 ± 8 et 69 ± 8%, respectivement ($P < 0,05$), et on comptait 7 ± 1 et 20 ± 4 min respectivement ($P < 0,05$) jusqu'à un retour de T_1 à 90%. Avec une dose de 0,5 mg · kg^{-1}, le temps d'installation était aussi plus court pour les cordes vocales (1,4 ± 0,1 min) que pour l'adducteur du pouce (2,4 ± 0,2 min, $P < 0.001$). On retrouvrait un bloc maximum de 77 ± 5 et 98 ± 1%, respectivement, et une durée d'action jusqu'à une récupération de T_1 à 90% de 22 ± 3 et 37 ± 4 min respectivement ($P < 0,01$). On en conclut que le rocuronium agit plus rapidement au niveau des muscles adducteurs du larynx, mais que le bloc neuromusculaire est moins intense qu'au niveau de l'adducteur de pouce. Ces résultats sont comparables à ceux obtenus avec le vécuronium, sauf que le rocuronium agit plus rapidement au niveau des deux muscles.

Key words
MONITORING: neuromuscular blockade;
NEUROMUSCULAR RELAXANTS: rocuronium;
SKELETAL MUSCLE: adductor pollicis, larynx.

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Neuromuscular blockade occurs more rapidly at the adductor muscles of the larynx than at the adductor pollicis, after injection of either vecuronium[1] or succinylcholine.[2] However, the dose of vecuronium required for laryngeal muscle blockade is larger than for comparable adductor pollicis blockade.[1] For succinylcholine, the opposite is true: less drug is required for laryngeal blockade.[2] When compared with vecuronium, succinylcholine has a faster onset of action at the adductor pollicis. Its onset of action at the laryngeal muscles (<1 min)[2] is also more rapid than that of vecuronium at the same muscle (3 min).[1]

Rocuronium (ORG 9426) is a new nondepolarizing muscle relaxant structurally similar to vecuronium.[3] Its onset of action at the adductor pollicis appears to be faster than that of vecuronium,[3,4] and the drug could be used to facilitate tracheal intubation. However, relaxation of the vocal cords is more important in obtaining excellent intubating conditions than paralysis of the adductor pollicis is.

Therefore, the aim of this study was to determine the onset time, intensity, and duration of action of rocuronium-induced neuromuscular blockade on both the laryngeal adductors and the adductor pollicis muscles in humans.

Methods

The protocol was approved by the Hospital Ethics Committee. Fourteen ASA I or II patients, 24–63 yr old, undergoing elective surgical procedures, were studied after giving informed consent. Exclusion criteria included abnormal upper airway, previous head and neck surgery or radiotherapy, and deviation from ideal body weight by more than 20%. No patient had any disease or was taking drugs known or suspected to interfere with neuromuscular transmission. Patients with cardiovascular, respiratory, hepatic or renal disease were also excluded from the study.

No premedication was used. On arrival in the operating room, ECG electrodes were applied and oxygen saturation was monitored by pulse oximetry. Blood pressure was monitored noninvasively with a cuff attached to the arm not involved with neuromuscular monitoring. Anaesthesia was induced with propofol (2–2.5 mg · kg^{-1}) and fentanyl (3–5 μg · kg^{-1}). Intubation was performed without neuromuscular relaxants and no local anaesthetic drug was given intratracheally. The system to monitor contraction of laryngeal adductor muscles has been described elsewhere.[5] Briefly, a Mallinckrodt tracheal tube (Athlone, Ireland) size 7.5 mm ID was used. The inflatable cuff of the tracheal tube was positioned between the vocal cords under direct vision. Then, it was inflated with air to 10–12 mmHg. The lungs were ventilated mechanically to maintain end-tidal carbon dioxide tension between 30–40 mmHg. Anaesthesia was maintained with propofol (10–15 mg · kg^{-1} · hr^{-1}) and intermittent boluses of fentanyl (1–2 μg · kg^{-1}). The use of nitrous oxide or halogenated agents was avoided.

Bilateral adduction of the vocal cords was produced by supramaximal stimulation of the recurrent laryngeal nerve over the notch of the thyroid cartilage, using 2 Hz train-of-four (TOF) stimulation every ten seconds.[5] The response of the laryngeal adductor muscles was evaluated by measuring the pressure change produced in the cuff of the tracheal tube by the adduction of the vocal cords. The ulnar nerve was stimulated at the wrist using supramaximal TOF every ten seconds. The force of contraction of the adductor pollicis was measured with a force transducer. Responses from both the laryngeal adductor muscles and adductor pollicis were displayed on an oscilloscope and recorded simultaneously on paper.

Patients were randomly allocated to receive a bolus of rocuronium of either 0.25 ($n = 7$) or 0.50 ($n = 7$) mg · kg^{-1}. Rocuronium was injected *iv* after a stable baseline had been obtained. Recordings were continued until recovery of the first twitch response (T_1) to 90% of control. Then, another neuromuscular relaxant (usually vecuronium) was given, the tracheal tube cuff was positioned deeper in the trachea, and the rest of the anaesthetic was left to the anaesthetist's discretion.

Onset time for both muscles was defined as the time from the end of the injection until maximum blockade of the first twitch response (T_1) of the TOF. When maximum blockade was attained at both muscles, the interval between TOF stimulations was increased to 20 sec. Times from injection to 25, 50, 75 and 90% T_1 recovery were determined for both muscles. The results are expressed as means ± standard error of the mean (SEM). A Student's t test for paired data was used to compare the data obtained at the vocal cords and the adductor pollicis. Dose-response curves were constructed from the logit transformation of maximum T_1 depression versus the logarithm of dose, then the ED_{50} and ED_{90} were derived for each muscle. The ED_{50} and ED_{90} are given as estimates ± standard error of estimate for the mean. Analysis of covariance was used to compare the dose-response data of the two muscles. A P value of 0.05 or less was considered to indicate statistically significant differences.

Results

Demographic data are summarized in Table I. Age, height and weight did not differ significantly between the two groups. Maximum neuromuscular blockade occurred sooner at the vocal cords than at the adductor pollicis with either dose (Figures 1 and 2). With 0.25 mg · kg^{-1} onset time was 3.0 ± 0.3 and 1.6 ± 0.1 min at the adductor pollicis and the laryngeal adductor muscles respectively (P

TABLE I Demographic data (± SEM when applicable)

Dose (mg · kg^{-1})	Sex (F/M)	Age (yr)	Weight (kg)	Height (cm)
0.25	7/0	48 ± 6	55 ± 3	159 ± 2
0.5	7/0	50 ± 3	62 ± 4	158 ± 2

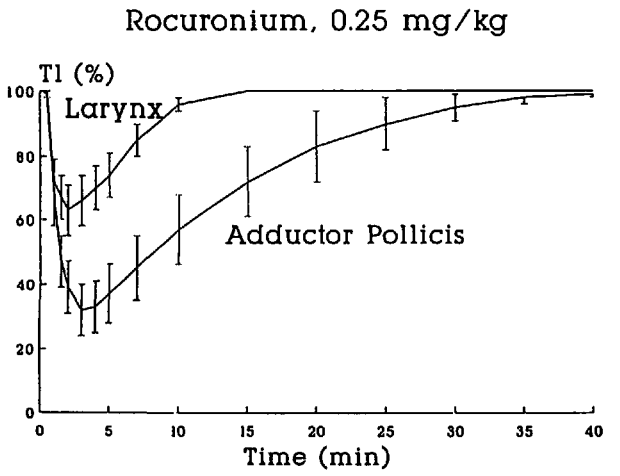

FIGURE 1 First twitch height (T_1) as a percentage of control, versus time after injection of rocuronium, 0.25 mg · kg^{-1}.

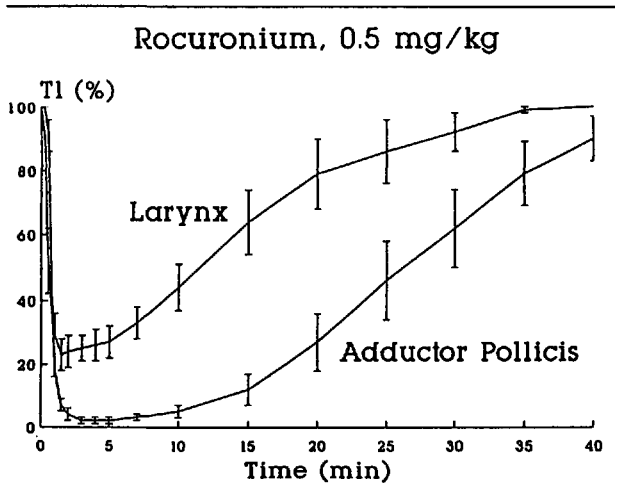

FIGURE 2 First twitch height (T_1) as a percentage of control, versus time after injection of rocuronium, 0.5 mg · kg^{-1}.

< 0.01). After 0.5 mg · kg^{-1} onset time was 2.4 ± 0.2 and 1.4 ± 0.1 min respectively ($P < 0.001$). Maximum blockade was significantly greater at the adductor pollicis than at the vocal cords for both doses (Table II; Figures 1 and 2). In all patients except one receiving 0.25 mg · kg^{-1} blockade was more intense at the adductor pollicis than at the vocal cords. With both doses recovery was much more

TABLE II Onset characteristics (mean ± SEM)

	Maximum blockade (%)		Onset time (min)	
	Larynx	Add poll	Larynx	Add poll
Rocuronium 0.25 mg · kg^{-1}	37 ± 8	69 ± 8	1.6 ± 0.1	3.0 ± 0.3
Vecuronium* 0.04 mg · kg^{-1}	55 ± 8	89 ± 3	3.3 ± 0.1	5.7 ± 0.2
Rocuronium 0.5 mg · kg^{-1}	77 ± 5	98 ± 1	1.4 ± 0.1	2.4 ± 0.2
Vecuronium* 0.07 mg · kg^{-1}	88 ± 4	98 ± 1	3.3 ± 0.2	5.7 ± 0.3

*Vecuronium data from Donati *et al.*[1]

rapid at the vocal cords than at the adductor pollicis (Table III; Figures 1 and 2). The dose-response curves did not deviate significantly from parallelism but the vocal cord response was shifted to the right. The ED_{50} was 0.318 ± 0.029 mg · kg^{-1} at the laryngeal adductor muscles and 0.208 ± 0.016 mg · kg^{-1} at the adductor pollicis ($P < 0.05$). Corresponding values for the ED_{90} were 0.684 ± 0.062 and 0.309 ± 0.023 mg · kg^{-1} respectively ($P < 0.05$).

Discussion

Our results demonstrate that after a single bolus dose of rocuronium, laryngeal adductor blockade is less than at the adductor pollicis, but time to maximal blockade is faster at the larynx. Recovery of laryngeal muscles is more rapid than that of the adductor pollicis. These results are qualitatively similar to those obtained with vecuronium under similar conditions,[1] but important quantitative differences remain. Onset to maximum blockade was markedly shorter for rocuronium both at the adductor pollicis and larynx (Table II). After injection of rocuronium, laryngeal muscles achieved maximal blockade after only 1.5 min. This interval was shorter than with vecuronium (3.3 min) (Table II), and only slightly more than after succinylcholine (0.9 min).[2]

The relatively short onset of action for rocuronium at the adductor pollicis has been reported in humans.[3,4,6] The present study also demonstrates a rapid onset at the laryngeal muscles. This indicates that the shorter onset time of rocuronium compared with vecuronium is present also at muscles other than the adductor pollicis, and could be observed at most, if not all, muscles. The reason for this rapid onset of action of rocuronium could be related to potency.[7] Injection of a low potency drug entails the presence of more relaxant molecules in the blood stream, leading to a faster occupancy of the number of receptors necessary to produce neuromuscular blockade.[8] This relationship between potency and onset time has been found in the cat,[9] and in humans.[10] The ED_{50} for rocuronium at the adductor pollicis was 0.205 μg · kg^{-1} in this

TABLE III Recovery characteristics (mean ± SEM)

	Larynx – duration to (min)				*Adductor pollicis – duration to (min)*			
	25%	*50%*	*75%*	*90%*	*25%*	*50%*	*75%*	*90%*
Rocuronium 0.25 mg · kg^{-1}	–	–	–	7 ± 1	–	–	–	10 ± 4
Vecuronium* 0.04 mg · kg^{-1}	–	–	–	11 ± 2	11 ± 2	16 ± 1	20 ± 2	26 ± 2
Rocuronium 0.5 mg · kg^{-1}	8 ± 3	13 ± 3	18 ± 3	22 ± 3	22 ± 3	27 ± 3	32 ± 3	37 ± 4
Vecuronium* 0.07 mg · kg^{-1}	9 ± 2	14 ± 2	19 ± 2	22 ± 3	22 ± 2	28 ± 2	34 ± 2	40 ± 3

*Vecuronium data from Donati *et al.*

– Blockade was too small to obtain several recovery indices.

study, comparable to the findings of other investigators.[3,4,6] It is approximately one seventh as potent as vecuronium. This potency ratio also applies to laryngeal muscles. The effect of rocuronium, 0.5 mg · kg^{-1}, is approximately equal to that of vecuronium, 0.07 mg · kg^{-1} (Table II).

After either vecuronium or rocuronium, laryngeal muscles demonstrated a "sparing" effect. For both doses given, maximum blockade was less at the larynx. Estimated ED_{50} was 1.52 times larger at the larynx than at the adductor pollicis, and this figure is comparable to the 1.73 times obtained with vecuronium.[1] This is in contrast to the greater degree of blockade obtained at the larynx after succinylcholine.[2] The reason for the resistance of the laryngeal muscles to the effect of nondepolarizing blockers, and its relative sensitivity to succinylcholine, is unknown. However, muscle type might play a role. For example, the thyroarytenoid, one of the muscles involved in closure of the glottis, has fast contraction times,[11] whereas the adductor pollicis is made up mostly of slow fibres.[12] Nondepolarizing neuromuscular blockers tend to produce less blockade at fast-twitch than slow-twitch fibres in the cat,[13] pig,[14,15] and human.[16] This difference in sensitivity of different types of muscle might be due to the larger number of acetylcholine receptors in fast-twitch fibres. Rat extensor digitorum longus, a fast muscle, has been found to have a greater acetylcholine receptor density than the soleus, a slow muscle.[17] If this finding can be generalized to all slow and fast muscles, it follows that more receptors need to be occupied to block a fast muscle. This suggests that potency of the neuromuscular blocking drug might be more important as a determinant of onset time in fast, resistant muscle than in slow, sensitive muscle.

In cat experiments, the sensitivity to various nondepolarizing muscle relaxants was tested on laryngeal and peripheral muscles.[18] Although the numbers were small, there was a suggestion that the sensitivity of laryngeal muscles compared with peripheral muscle might vary according to the agent used. Lu arrived at the same conclusion when comparing the diaphragm with peripheral muscle.[19] Thus, it might be theoretically possible to have "larynx specific" non-depolarizing relaxants in humans. This category of agents would include neither vecuronium nor rocuronium. Although the concept might appear attractive, it must be stressed that vocal cord relaxation is not the only requirement for excellent intubating conditions, and an agent given in a dose sufficient to produce paralysis in all muscles would probably be more useful clinically. Furthermore, the sensitivity of a given muscle group to a given drug might also be species-specific, and animal data do not *a priori* apply to humans.

Recovery characteristics were found to be similar with rocuronium and vecuronium. When equipotent doses are used (0.5 mg · kg^{-1} and 0.07 mg · kg^{-1}, respectively), times to 25, 50, 75 and 90% recovery are approximately the same, both at the larynx and the adductor pollicis (Table III). Thus, rocuronium appears to have an intermediate duration neuromuscular blocking drug, comparable with that of vecuronium.

The onset time of neuromuscular blockade at the laryngeal adductor muscles after rocuronium 0.50 mg · kg^{-1} (1.5 ± 0.1 min) is close to the onset time following succinylcholine (0.9 ± 0.1 min).[2] These results suggest that rocuronium can be used when adequate intubating conditions are required rapidly, maximum blockade being obtained in approximately 1.5 min. However, 90% blockade at the laryngeal muscles is obtained with relatively high doses (0.684 mg · kg^{-1}), and excellent intubating conditions might not be present in all patients unless even higher doses are given, especially if laryngoscopy is performed as early as 60 sec after injection of the relaxant drug. In this respect, succinylcholine probably has an added advantage: vocal cord relaxation is produced at relatively low doses (less than 0.5 mg · kg^{-1}). In addition, its duration of action is much shorter than that

of rocuronium, which implies that failed intubation is easier to manage if succinylcholine has been used.

Monitoring the adductor pollicis during onset of blockade to determine the time required for good intubating conditions to be achieved could be misleading because paralysis of the adductor pollicis lags behind onset of neuromuscular blockade at the vocal cords. Furthermore the adductor pollicis may be blocked with a dose which could be insufficient to block the laryngeal adductor muscles because the latter are more resistant to rocuronium.

In conclusion, rocuronium is a new nondepolarizing relaxant with a rapid onset of action, particularly at the vocal cords. This drug could be a valuable alternative to succinylcholine when good intubating conditions are required rapidly. Its duration of action is similar to that of vecuronium, both at the adductor pollicis and laryngeal adductor muscles.

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