Pharmacokinetics and pharmacodynamics of rocuronium at the vocal cords and the adductor pollicis in humans

The pharmacokinetic-pharmacodynamic relationship of rocuronium at the laryngeal adductor muscles and the adductor pollicis was determined in eight patients during general anesthesia. Rocuronium was administered as an infusion at a rate of 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ over 5 minutes. The half-life of transport between plasma and biophase (effect compartment) was significantly shorter at the adductor laryngeal muscles (2.7 ± 0.6 minutes, mean ± SD) than at the adductor pollicis (4.4 ± 1.5 minutes, $p = 0.003$). The concentration in the effect compartment producing 50% of the maximum effect was significantly greater at the adductor laryngeal muscles (1424 ± 148 $\mu g \cdot L^{-1}$) than at the adductor pollicis (823 ± 157 $\mu g \cdot L^{-1}$, $p = 0.0001$). The shorter onset of neuromuscular blockade at the laryngeal muscles than at the adductor pollicis may be explained by a faster transfer rate at the laryngeal adductor muscles neuromuscular junction than at the adductor pollicis neuromuscular junction. (CLIN PHARMACOL THER 1995;58:185-91.)

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Rocuronium (2-morpholino, 16-ally-pyrrollidino, 3-desacetyl derivative of vecuronium) is a new nondepolarizing steroidal muscle relaxant with a shorter onset of action[1,2] than currently available muscle relaxants. It has been shown that the onset of action of rocuronium was shorter at the laryngeal adductor muscles than at the adductor pollicis.[3] It has been suggested that this faster onset might be related to a relatively higher blood flow to the laryngeal muscles compared with the peripheral muscles. Moreover, intensity of effect is less at the laryngeal muscles compared with the adductor pollicis.[3] These data suggest that a higher concentration of rocuronium is required to block the laryngeal adductors muscles compared with the adductor pollicis but that the rate of transfer (k_{eo}) is faster at the laryngeal muscles than at the adductor pollicis. However, the numeric value of these data cannot be obtained and this hypothesis cannot be confirmed unless rocuronium plasma concentrations (pharmacokinetics) have been measured. The aim of this study was to determine simultaneously the pharmacokinetics and the pharmacodynamics of rocuronium at both the laryngeal adductor muscles and the adductor pollicis in humans and thereby determine if the pharmacodynamic differences might be explained by differences in the pharmacokinetic-pharmacodynamic relationship.

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METHODS

The protocol was approved by the Committee on Human research. Eight patients (American Society of Anesthesiologists class I or II; age range, 31 to 58 years) I or II; scheduled for elective nonhemorrhagic surgery were studied after each gave written informed consent. Exclusion criteria were neuromuscular disease; concurrent administration of any drug known or suspected to interfere with neuromuscular transmission; renal, cardiac, pulmonary, or hepatic failure; and

electrolyte abnormality. When the subject arrived in the operating room, ECG, pulse oximetry, arterial blood pressure, and central core temperature were monitored noninvasively. No premedication was used. Anesthesia was induced intravenously with propofol (2 to 2.5 mg · kg^{-1}) and alfentanil (20 to 30 μg · kg^{-1}). The trachea was intubated without muscle relaxant, and the cuff of the tracheal tube was positioned between the vocal cords under direct vision.[4] The lungs were then ventilated mechanically with oxygen (100%) to maintain end-tidal Co_2 within a normal range (4 to 5 kPa). Anesthesia was maintained with propofol (5 to 10 mg · kg^{-1} · hr^{-1}) and intermittent doses of alfentanil (10 to 20 μg · kg^{-1}) intravenously. The use of nitrous oxide and halogenated agents was avoided.

The ulnar nerve was stimulated through surface electrodes at the wrist with use of supramaximal train-of-four stimulations (four pulses of 0.2 msec in duration, at a frequency of 2 Hz every 10 seconds). The elicited force of the adductor pollicis was recorded with a force transducer. The recurrent laryngeal nerve was stimulated by train-of-four stimulations through surface electrodes placed over the notch of the thyroid cartilage. The response of the laryngeal adductor muscles was measured as the pressure changes in the cuff of the tracheal tube.[4] The response of both muscles was displayed on a Gould V1000 (Gould Instrument Systems Inc., Valley View, Ohio) and recorded simultaneously on paper with a Gould ES1000 chart recorder. The effect was defined as the percentage of depression of the first twitch (T1) compared to the control value (T0) before rocuronium injection. The time to reach maximum effect was defined as the interval between start of infusion and maximum T1 blockade. Time from start of infusion to 25%, 50%, 75%, and 90% T1 recovery was also measured.

When anesthesia and the recordings were stable at both the adductor pollicis and laryngeal muscles, rocuronium was infused at a rate of 100 μg · kg^{-1} · min^{-1} over 5 minutes at the arm opposite to measurement of neuromuscular blockade. Blood samples (4 ml) were drawn from an arterial line 0, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 20, 30, 45, 60, 90, 120, 180, 240, 300, and 360 minutes after the start of the infusion. Each sample was transferred into lithium-heparinized tube containing 1 ml monobasic sodium phosphate 1 mol/L to avoid hydrolysis of rocuronium. The samples were centrifuged immediately, then plasma was frozen at −80° C and stored until analysis. Concentrations of rocuronium and its potential metabolites, 17-desacetylrocuronium and desallylrocuronium were analyzed by HPLC as previously described.[5] The accuracy, given in percentages of the added amount and coefficient of variation (CV), of 10 and 200 ng rocuronium were 117.7% (CV, 23.0) and 101.6% (CV, 5.1), respectively. The precision of the analysis is expressed in the CV of the calibration curves. The mean value of the CV was 8%. The lower limit of quantification of the method, defined as the minimum amount that can be determined with an accuracy and precision better than 15%, was 10 ng · ml^{-1}.

The plasma concentration–time data were analyzed by use of the program MultiFit.* For each individual patient the parameters of an open two- and three-compartment model were fitted to the logarithm of the plasma concentration–time data pairs, taking into account a constant infusion rate and assuming a constant relative error. The correctness of this assumption was tested by visual inspection of the graphs of the residuals plotted against time and against the concentration. The optimization procedure was performed at least twice, with the simplex algorithm[6] and the Marquardt algorithm,[7] respectively, with use of initial estimates obtained by a curve-stripping procedure. The choice between two- and three-compartment models was based on the F test,[8] accepting a more complex model as significantly better fitting if $p \leq 0.05$, and on the lowest value of Akaike's information criterion.[9] The volume of the central compartment, the steady-state volume of distribution, and the plasma clearance were calculated with standard equations,[10] assuming that elimination takes place from the central compartment.[10]

The effect (twitch height in the adductor muscles of the larynx and adductor pollicis–time data were analyzed with use of the program PkPdFit.* For each individual patient and each muscle type the parameters of the pharmacokinetic-pharmacodynamic model according to Sheiner model,[11] i.e., the rate constant of transport between the plasma and effect compartments (k_{eo}), the concentration producing 50% block (EC_{50}), and the sigmoidicity coefficient of the Hill equation (γ), were fitted to the effect (measured as T1 depression as a percentage of control value), using equal weight for each measurement (assuming constant absolute error). For each individual patient, the kinetic parameters (slopes and intercepts of the plasma concentration–time curve) associated with the best-fitting model were used. The optimization procedure was performed at least twice, with the simplex algorithm[6]

*MultiFit and PkPdFit can be obtained on request from Johannes H. Proost, University Center for Pharmacy, University of Groningen, Groningen, The Netherlands.

Table I. Individual demographic data

Patient	*Age (yr)*	*Weight (kg)*	*Height (cm)*	*Gender*
1	48	45	157	Female
2	58	64	164	Female
3	54	67	168	Male
4	55	60	161	Female
5	45	59	168	Female
6	31	72	174	Male
7	49	53	162	Female
8	39	53	168	Female
Mean ± SD	47 ± 9	59 ± 9	165 ± 5	6 Females 2 Males

Table II. Onset and recovery characteristics at the adductor muscles of the larynx and the adductor pollicis

Variable	*Larynx*	*Adductor pollicis*	*p Value*
Maximum blockade (%)	72 ± 11	95 ± 9*	0.0003
Onset (min)	5.8 ± 1.3	7.1 ± 2.5*	0.048
25% Recovery (min)	7.9 ± 0.9	22.1 ± 5.1	—
50% Recovery (min)	12.9 ± 2.8	25.1 ± 6.6*	0.005
75% Recovery (min)	20.1 ± 4.0	30.2 ± 6.1*	0.0008
90% Recovery (min)	24.5 ± 6.5	32.7 ± 8.2*	0.006

Data are mean values ± SD.
*$p < 0.05$ or less compared with the adductor pollicis.

and the Marquardt algorithm,[7] respectively, with use of various sets of initial estimates (e.g., the results obtained from the previous patient or mean values for all patients in larynx or adductor pollicis).

The results are expressed as means values ± SD. Comparisons between values obtained from the adductor laryngeal muscles and the adductor pollicis were performed with use of a paired Student *t* test. A *p* value ≤0.05 was considered to indicate statistically significant differences.

RESULTS

Individual demographic data are presented in Table I. Maximum neuromuscular block was significantly less intense at the adductor muscles of the larynx (72% ± 11%) than at the adductor pollicis muscle (95% ± 9%, $p = 0.0003$; Table II). The onset time at the adductor laryngeal muscles (5.8 ± 1.3 minutes) was significantly shorter than at the adductor pollicis muscle (7.1 ± 2.5 minutes, $p = 0.048$). Recovery was significantly more rapid at the adductor muscles of the larynx than at the adductor pollicis. Time to 90% recovery was 24.5 ± 6.5 minutes at the adductor muscles of the larynx, compared with 32.7 ± 8.2 minutes at the adductor pollicis ($p = 0.006$).

The pharmacokinetic variables are presented in Table III as mean values and SD. The potential metabolites of rocuronium were not detected in any of the patients. Mean arterial rocuronium plasma concentrations versus time are presented in Fig. 1. The calculated variables for the pharmacokinetic-pharmacodynamic relationship are presented in Table IV. The concentration-effect relationship led to significant hysteresis for both muscles (Fig. 2). Fig. 3 shows an example of curve fitting at the adductor muscles of the larynx and the adductor pollicis. The value of k_{eo} was significantly greater at the laryngeal muscles than at the adductor pollicis: 0.260 ± 0.060 versus 0.168 ± 0.063 min^{-1}, respectively ($p = 0.006$). The half-life of transport between the plasma and effect compartments ($t_{1/2}k_{eo}$) was significantly shorter at the adductor laryngeal muscles than at the adductor pollicis: 2.7 ± 0.6 versus 4.4 ± 1.3 minutes, respectively ($p = 0.003$). The EC_{50} was significantly greater at the adductor laryngeal muscles (1424 ± 148 $\mu g \cdot L^{-1}$) than at the adductor pollicis (823 ± 157 $\mu g \cdot L^{-1}$, $p = 0.0001$). The slope factor (γ) was significantly different between the laryngeal adductor muscles and the adductor pollicis: 2.94 ± 0.87 versus 4.79 ± 1.70, respectively ($p = 0.04$).

Table III. Rocuronium pharmacokinetics parameters after an infusion of 500 $\mu g \cdot kg^{-1}$ rocuronium

Parameters	*Mean ± SD*
Terminal $t_{1/2}$ (min)	46 ± 22
CL ($ml \cdot kg^{-1} \cdot min^{-1}$)	9.78 ± 3.04
V_C ($L \cdot kg^{-1}$)	0.056 ± 0.026
V_{SS} ($L \cdot kg^{-1}$)	0.285 ± 0.118

$t_{1/2}$, Half-life; CL, total plasma clearance; V_C, volume of the central compartment; V_{SS}, steady-state volume of distribution.

DISCUSSION

This study shows that the apparent k_{eo} of rocuronium between plasma and biophase is faster at the laryngeal adductor muscles than at the adductor pollicis and that the EC_{50} is greater at the laryngeal adductor muscles than at the adductor pollicis.

The greater k_{eo} at the laryngeal muscles might explain in turn the faster onset of action of neuromuscular block at the adductor laryngeal muscles than at the adductor pollicis. The k_{eo} of rocuronium at the adductor pollicis is 1.8 times the value observed with atracurium in comparable conditions of anesthesia and

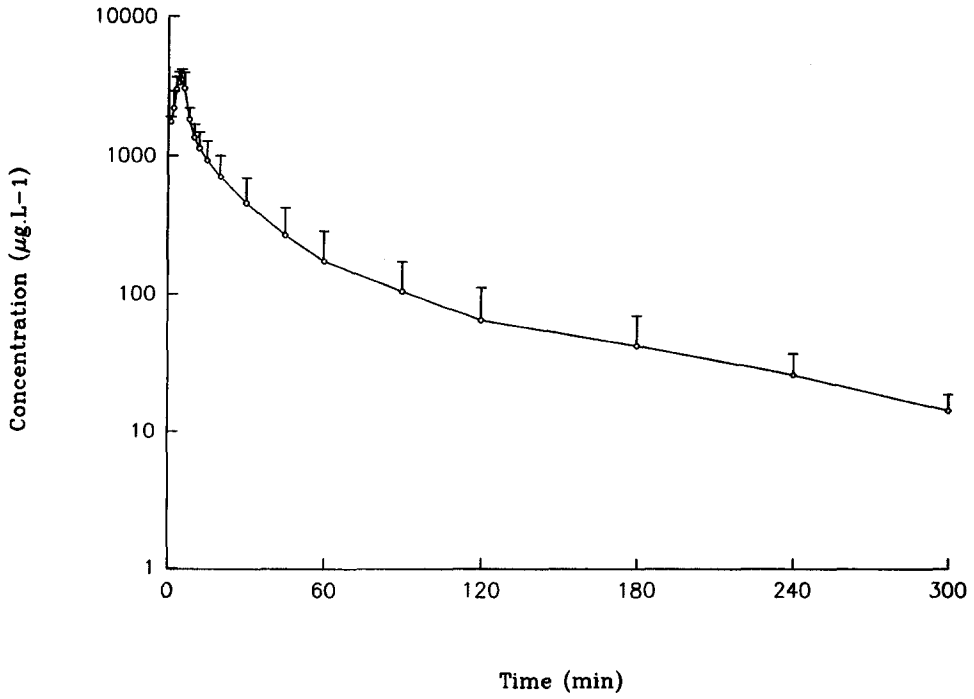

Fig. 1. Mean arterial rocuronium plasma concentration (log scale) versus time (n = 8). *Bars* indicate SD.

Table IV. Parameters of the pharmacokinetic-pharmacodynamic relationship at the adductor muscles of the larynx and at the adductor pollicis

	k_{eo} (min^{-1})		$t_{1/2}k_{eo}$ (min)		EC_{50} ($\mu g \cdot L^{-1}$)		γ	
Patient No.	*Adductor muscles of the larynx*	*Adductor pollicis*	*Adductor muscles of the larynx*	*Adductor pollicis*	*Adductor muscles of the larynx*	*Adductor pollicis*	*Adductor muscles of the larynx*	*Adductor pollicis*
1	0.225	0.136	3.0	4.9	1479	1038	2.44	5.13
2	0.322	0.173	2.1	3.9	1496	721	3.10	3.25
3	0.240	0.125	2.8	5.4	1560	881	3.91	4.94
4	0.267	0.130	2.5	5.2	1530	813	2.54	3.24
5	0.374	0.225	1.8	3.0	1342	855	2.57	6.02
6	0.239	0.296	2.8	2.3	1556	819	2.58	8.18
7	0.231	0.152	2.9	4.4	1173	512	1.87	3.62
8	0.184	0.106	3.7	6.3	1254	943	4.51	3.92
Mean ± SD	0.260 ± 0.06	0.168 ± 0.063	2.7 ± 0.6	4.4 ± 1.3	1424 ± 148	823 ± 157	2.94 ± 0.87	4.79 ± 1.70
p Value	0.006		0.003		0.0001		0.04	

k_{eo}, Rate constant of transport between the plasma and effect compartments; $t_{1/2}k_{eo}$, half-life of transport between the plasma and effect compartments; EC_{50}, concentration producing 50% block; γ, sigmoidicity coefficient of the Hill equation.

sampling.[12] The k_{eo} of rocuronium at the adductor pollicis seems to be greater than the value observed with vecuronium (0.10 min^{-1}) with use of venous sampling.[13] This rapid onset of action might be related to potency because administration of a low-potency drug, such as rocuronium, 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 block.[14,15] Donati et al.[12] recently demonstrated that the venous levels of neuromuscular relaxants were lower than corresponding arterial values for up to 20 minutes and that the determination of the k_{eo} was influenced strongly by this gradient of concentration. It is therefore preferable to

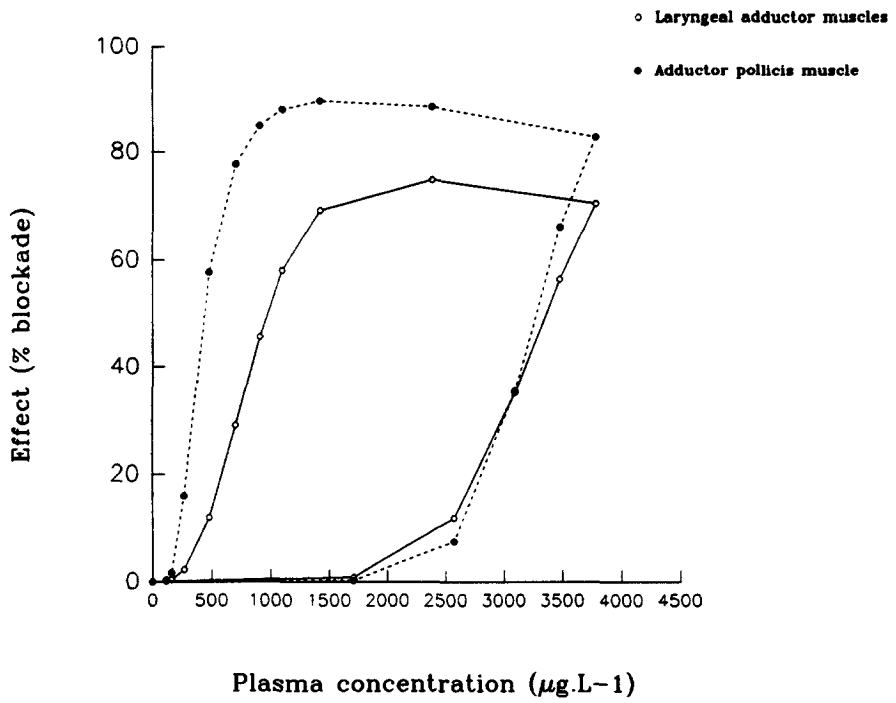

Fig. 2. Neuromuscular blockade in percentage of the control value at the adductor laryngeal muscles and at the adductor pollicis muscle versus plasma concentration in patient 4.

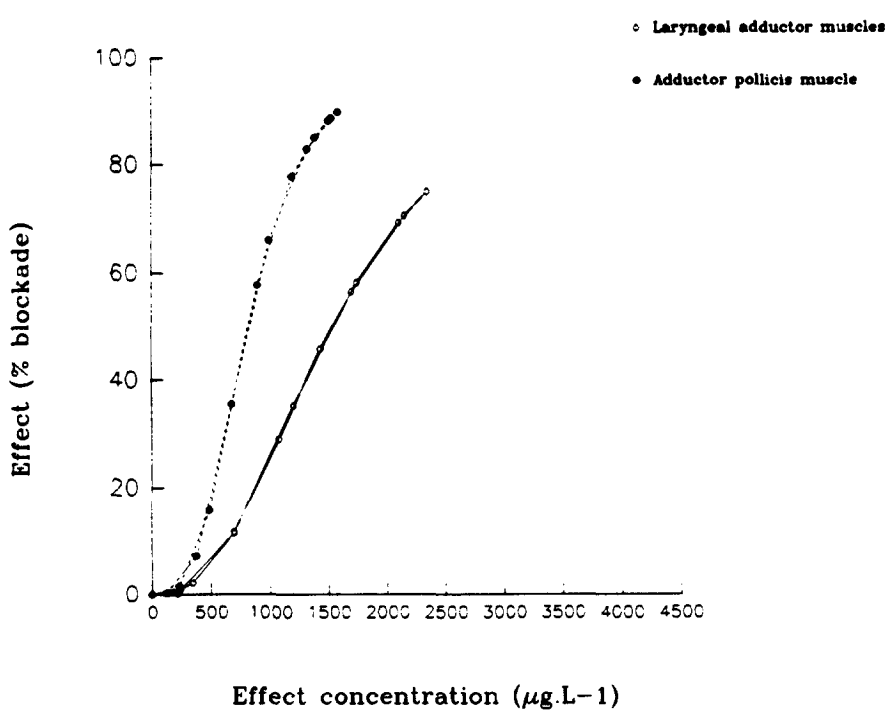

Fig. 3. Neuromuscular blockade in percent of the control value at the adductor laryngeal muscles and at the adductor pollicis muscle versus calculated concentration in the effect compartment in patient 4 (best fit).

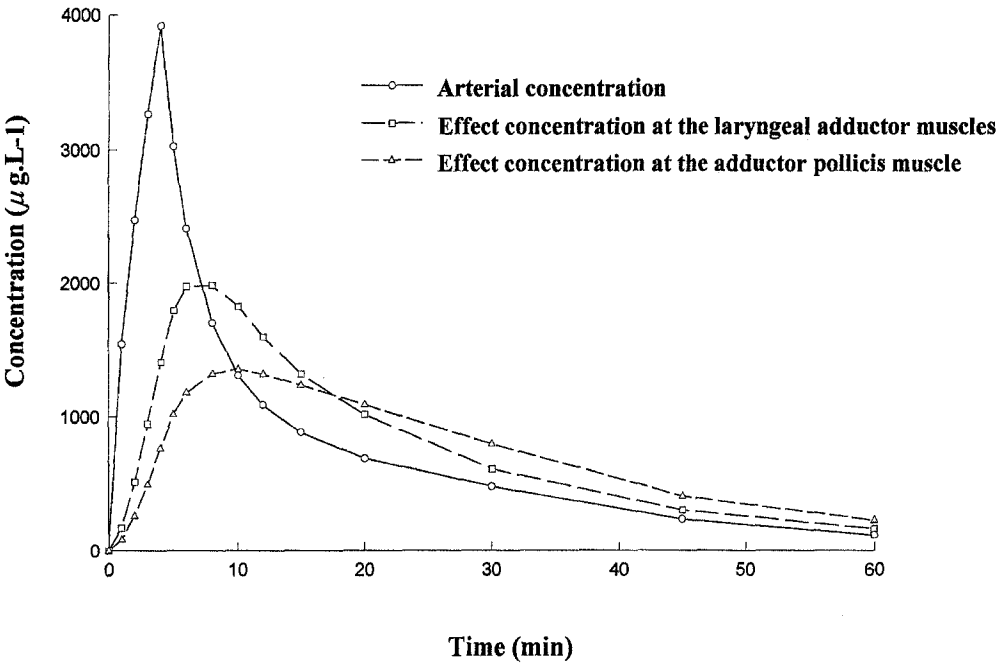

Fig. 4. Rocuronium plasma concentration and calculated concentration in the effect compartment at the adductor laryngeal muscles and the adductor pollicis muscle versus time in patient 4.

use an arterial sampling site to determine the pharmacokinetic-pharmacodynamic relationships when two different muscles must be compared.

Previous pharmacodynamic studies have shown that the laryngeal muscles are more resistant to the effects of nondepolarizing muscle relaxants than the adductor pollicis.[3,16,17] The estimated ED_{50} is 1.52 times larger at the larynx than at the adductor pollicis for rocuronium.[3] This ratio is close to the ratio of the EC_{50} (1.73) obtained in our study. The reason for the resistance of the laryngeal adductor muscles to nondepolarizing muscle relaxants remains speculative. The laryngeal adductor muscles are mostly made of fast contraction time fibers. These fibers are more resistant to muscle relaxants than slow-twitch fibers, which are abundant in the peripheral muscles such as the adductor pollicis.[18] These differences in sensitivity of different types of muscular fibers might be due to the large numbers of cholinergic receptors in fast-twitch fibers.[19]

After administration of a bolus dose, rocuronium-induced maximum block occurs sooner at the laryngeal adductor muscles than at the adductor pollicis; however, maximum blockade is significantly less intense at the laryngeal muscles than at the adductor pollicis. These discrepancies in time course and intensity of neuromuscular block might be explained by the differences in muscle-related pharmacokinetic-pharmacodynamic relationship differences. After administration of a bolus dose, rocuronium concentration at the neuromuscular junction increases more rapidly at the laryngeal adductor muscles than at the adductor pollicis (Fig. 4) because the k_{eo} is greater at the laryngeal muscles. Maximum block at the laryngeal muscles occurs sooner than at the adductor pollicis. Therefore concentrations corresponding to maximum block at the laryngeal muscles are greater than at the adductor pollicis. These findings are confirmed by the greater value of the EC_{50} at the laryngeal muscles than the adductor pollicis.

Meistelman et al.[3] have reported that recovery from rocuronium-induced neuromuscular block is significantly faster at the laryngeal adductor muscles than at the adductor pollicis. The greater EC_{50} at the laryngeal muscles explain why they recover from neuromuscular block before the adductor pollicis does. Recovery from neuromuscular block is a very slow phenomenon compared with onset of paralysis, and it occurs during the elimination phase. During recovery, a pseudoequilibrium is reached between plasma and the neuromuscular junction at both muscles. Recovery occurs more rapidly at the larynx than the adductor pollicis because

lower blood concentrations must be achieved at the adductor pollicis, compared with the laryngeal adductor muscles, before recovery begins.

In conclusion, we have found muscle-related differences in the pharmacokinetic-pharmacodynamic relationship of rocuronium-induced neuromuscular block. The faster onset at the laryngeal adductor muscles than at the adductor pollicis might be explained by a greater k_{eo} at the laryngeal adductor muscles.

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