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ORG 9487 Neuromuscular Block at the Adductor Pollicis and the Laryngeal Adductor Muscles in Humans

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Background: ORG 9487 is a new steroidal nondepolarizing muscle relaxant with a rapid onset of action. This study was designed to determine the neuromuscular blocking profile of ORG 9487 at the adductor muscles of the larynx and the adductor pollicis.

Methods: In 30 adults, anesthesia was induced with propofol (2–5 mg/kg) and fentanyl (2–3 µg/kg). After train-of-four stimulation, the block of the laryngeal adductor muscles was evaluated by measuring the pressure changes in the cuff of the tracheal tube placed between the vocal cords, and the force of the contraction of the adductor pollicis was measured with a force transducer. Patients were randomly allocated to receive ORG 9487 at intravenous bolus doses of 0.75, 1.5 or 2 mg/kg (n = 10 in each group).

Results: Time to peak effect was significantly shorter at the vocal cords than at the adductor pollicis muscle ($P < 0.001$). Onset time at the vocal cords was 62 ± 16 s, 62 ± 13 s, and 52 ± 14 s (mean ± SD) after doses of 0.75, 1.5, and 2 mg/kg, respectively (not significant). Onset time at the adductor pollicis muscle was 126 ± 33 s, 96 ± 20 s, and 82 ± 21 s after 0.75, 1.5, and 2 mg/kg doses, respectively ($P < 0.001$). Maximum block was significantly less intense at the vocal cords than at the adductor pollicis muscle ($69 \pm 15\%$ *vs.* $94 \pm 4\%$ after 0.75 mg/kg; $86 \pm 7\%$ *vs.* $97 \pm 4\%$ after 1.5 mg/kg; and $91 \pm 5\%$ *vs.* $99 \pm 1\%$ after 2 mg/kg). After 1.5 mg/kg duration to 25%, recovery was 3.7 ± 2.2 min *versus* 10.2 ± 2.5 min at the vocal cords and the adductor pollicis muscle, respectively, and 75% recovery occurred at 9.7 ± 3.7 min at the vocal cords and at 18.3 ± 5.2 min at the adductor pollicis muscle.

Conclusions: ORG 9487 has a rapid onset of action at the laryngeal adductor and the adductor pollicis muscles. Onset

and duration of action are faster at the vocal cords than at the adductor pollicis muscle. However, the maximum block obtained at the laryngeal muscles was less than at the adductor pollicis, regardless of the dose of ORG 9487. (Key words: Monitoring: neuromuscular blockade. Neuromuscular relaxant: ORG 9487. Skeletal muscles: adductor pollicis; laryngeal adductor muscles. Larynx: vocal cords.)

OTHER researchers have shown that ORG 9487, a new nondepolarizing steroidal muscle relaxant, has a rapid onset of action at the adductor pollicis muscle.[1] Its onset time is similar to that of succinylcholine (1 mg/kg). The effective dose expected to produce 90% blockade (ED_{90}) value has been estimated to be approximately 1.15 mg/kg bromide ion at the adductor pollicis.[2] The low potency is probably responsible for the short onset of action.[1] However, the duration of action of ORG 9487 is somewhat longer compared with succinylcholine: time from injection until 90% recovery of the first response at train-of-four response at the adductor pollicis was 16.4 and 10.6 min after administration of 1.5 mg/kg ORG 9487 and 1 mg/kg succinylcholine, respectively.[1]

Adequate relaxation of the laryngeal adductor muscles is required to obtain good intubating conditions because they are involved in the adduction of the vocal cords. Vecuronium and rocuronium are more potent at the adductor pollicis than at the laryngeal adductor muscles,[3,4] but the onset time of these two agents is faster at the laryngeal adductor muscles than at the adductor pollicis, albeit it is slower than after succinylcholine administration.[5] The onset time of neuromuscular blocking agents at the laryngeal muscles is mandatory to determine the appropriate delay for tracheal intubation. Thus, if ORG 9487 is a candidate to replace succinylcholine in the rapid induction sequence, the onset time and the maximum effect of this new compound at the laryngeal adductor muscles should be determined.

The aim of the study was to evaluate and compare

the time course of action of three different doses of ORG 9487 at the adductor muscles of the larynx and the adductor pollicis in humans.

Materials and Methods

The study was approved by the Ethics Committee of Université Paris-Sud. Informed written consent was obtained from all the patients included in the study. Thirty patients, who were classified as American Society of Anesthesiologists physical status I or II, aged 18 to 65 yr, and undergoing peripheral surgical procedures were studied. Patients with cardiovascular, respiratory, hepatic, renal, or neuromuscular disease were excluded from the study. Exclusion criteria also included abnormal upper airway,[6] previous head and neck surgery or radiotherapy, and deviation from ideal body weight by more than 20%. Patients were not taking drugs known or suspected to interfere with neuromuscular transmission.

No premedication was used. On arrival in the operating room, electric activity of the heart, pulse oximetry, and arterial blood pressure were monitored noninvasively. The blood pressure cuff was placed on the arm opposite that used for neuromuscular monitoring. Anesthesia was induced with propofol (2–5 mg/kg) and fentanyl (2 or 3 μg/kg). Intubation was performed without neuromuscular relaxant, and no local anesthetic drug was given intratracheally. The system to monitor contraction of laryngeal adductor muscles has been described elsewhere.[7] The inflatable cuff of the tracheal tube (7.5-mm inner diameter; Mallinckrodt, Athlone, Ireland) was positioned during laryngoscopy between the vocal cords, and the cuff was inflated with air to obtain a resting pressure of 10–12 mmHg. The lungs were ventilated mechanically to maintain end-tidal carbon dioxide tension between 30 and 40 mmHg. Anesthesia was maintained with propofol (10–15 mg·kg^{-1}·h^{-1}) and intermittent boluses of fentanyl (1 or 2 μg/kg). Nitrous oxide and halogenated agents were not used throughout the study. Surface electrodes were applied over the ulnar nerve at the wrist. The force of contraction of the adductor pollicis muscle was recorded using a force transducer (Bio Industry Curamètre Module 2, Boulogne sur Mer, France). To stimulate the recurrent laryngeal nerve, a negative electrode was placed on the notch of the thyroid cartilage, and a positive electrode was placed on the forehead. Vocal cord responses were evaluated by measuring the pressure change produced in the inflatable cuff of the tracheal tube using an air-filled transducer.[6] The responses from both sites were displayed on a Gould V1000 CRT and recorded simultaneously on paper with a Gould ES1000 chart recorder. Supramaximal train-of-four stimulations (pulse lasting 0.2 ms; 2 Hz lasting 2 s) were applied at the ulnar and the recurrent laryngeal nerves every 10 s. Because of the setup of the recording at the laryngeal adductor muscles, approximately 10 min were needed between the start of the stimulation and administration of the agent. Patients were randomly allocated to receive an intravenous ORG 9487 bolus (more than 5 s) at doses of either 0.75 (n = 10), 1.5 (n = 10), or 2 (n = 10) mg/kg. Data were recorded until a train-of-four ratio of 0.70 was obtained at the adductor pollicis muscle.

The following parameters were measured and calculated at both muscles: 1) the time from the end of injection of ORG 9487 until the first depression of the first twitch response (T1) of the train-of-four (lag time); 2) the amplitude of neuromuscular block 1 min after the injection of ORG 9487; 3) the intensity of maximum neuromuscular block; 4) the time from the end of injection of ORG 9487 until the maximum depression of T1 (onset time); 5) the time from the end of injection of ORG 9487 until 25% recovery of T1 response (REC 25); 6) the time from the end of injection of ORG 9487 until 75% recovery of T1 response (REC 75); 7) the time from 25% to 75% recovery of T1 response (recovery index); and 8) the time from the end of injection of ORG 9487 until 70% recovery of train-of-four ratio (REC train-of-four = 70), but only for the adductor pollicis muscle.

During recovery from neuromuscular block, all data recorded were normalized to the final first twitch of the train-of-four, as recommended by the Good Clinical Research Practice consensus conference.[8]

The results are expressed as means ± SD. For each dose, we used a Student's t test for paired data to compare the data obtained at the vocal cords and the adductor pollicis. To get an impression of the difference among patients between the two muscles groups for the different time course of action parameters, we made estimates with 95% confidence intervals for these differences. If case zero was not within the 95% confidence interval, we considered the difference to be significant from zero. For each muscle, we compared the doses using an analysis of variance and a Scheffé F test. A probability value of 0.05 or less was considered to indicate significant differences.

Results

Table 1 summarizes demographic data. Age, height, and weight did not differ significantly among the three

Table 1. Demographic Data

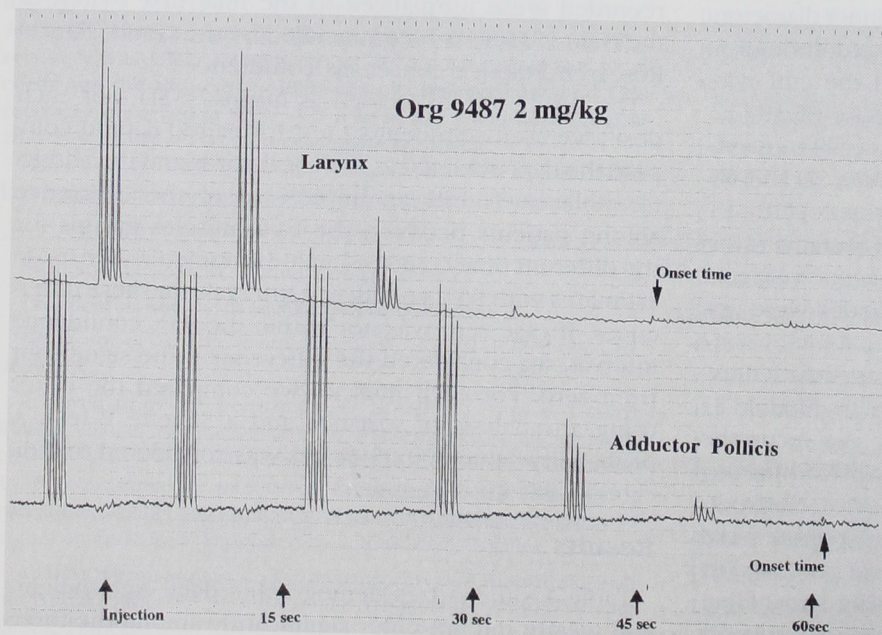| Dose (mg·kg⁻¹)	n	Age (yr)	Weight (kg)	Height (cm)
0.75	10	46 ± 8	60 ± 5	162 ± 7
1.5	10	50 ± 4	58 ± 8	159 ± 4
2.0	10	46 ± 9	59 ± 8	161 ± 4

Values are mean ± SD.

groups. Figure 1 shows a typical tracing. For each dose, the lag time and the onset time were significantly shorter at the vocal cords than at the adductor pollicis muscle ($P < 0.001$; table 2). Onset at the adductor pollicis decreased significantly when the dosage was increased (126 ± 33 s, $96 + 20$ s, and 82 ± 21 s after 0.75, 1.5, and 2 mg/kg, respectively; $P < 0.001$). In contrast, onset at the vocal cords did not decrease when increasing the dose (62 ± 16 s, 62 ± 13 s, and 52 ± 14 s after 0.75, 1.5, and 2 mg/kg, respectively). Maximum block was significantly greater at the vocal cords than at the adductor pollicis muscle for the three doses. One hundred percent block was not reached at the laryngeal adductor muscles regardless of the dosages. One hundred percent block at the adductor pollicis muscle was achieved in no, three, and eight patients after 0.75, 1.5, and 2 mg/kg doses, respectively. Recovery times (REC 25 and REC 75) were significantly shorter at the vocal cords than at the adductor pollicis muscle (table 3). Recovery index was not statistically different between the two muscles for a given dosage, but recovery index was lengthened when the dosage was increased (table 3).

Discussion

We found that the laryngeal adductor muscles are more resistant than the adductor pollicis to the neuromuscular blocking effects of ORG 9487. Onset time and duration of action are shorter at the laryngeal adductor muscles than at the adductor pollicis. The onset time of an ORG 9487-induced neuromuscular block is rapid[9] at the vocal cords, close to 1 min, at doses of 0.75 and 1.5 mg/kg, and it is ultrarapid (less than 1 min)[9] at a dose of 2 mg/kg.

The doses that we used were chosen to produce an incomplete block at the adductor pollicis and the laryngeal adductor muscles (0.75 mg/kg); complete block at the adductor pollicis and partial block at the vocal cords (1.5 mg/kg); and complete block at the adductor pollicis and the vocal cords (2 mg/kg), respectively. However, the intensity of the neuromuscular block at the adductor pollicis (94%, 97%, and 99% after 0.75, 1.5, and 2 mg/kg, respectively) in our study indicate that the ED₉₀ at the adductor pollicis muscle was lower than determined initially.[2] In a previous study,[2] the ED₉₀ of

Org 9487 2 mg/kg

Larynx

Onset time

Adductor Pollicis

Onset time

Injection   15 sec   30 sec   45 sec   60sec

Fig. 1. Response to train-of-four stimulation applied every 10 s at the recurrent laryngeal nerve (top) and ulnar nerve (bottom) after 2 mg/kg ORG 9487 (shown at the arrow). Onset of block was faster at the laryngeal adductor muscles than at the adductor pollicis. Maximum block occurred in 45 s at the larynx and in 60 s at the adductor pollicis muscle.

Table 2. Onset Characteristics

Variable	Dose (mg·kg⁻¹)	Larynx	Adductor Pollicis	Estimated Mean Difference*	95% Confidence Interval†
Lag time (s)	0.75	27 ± 9	42 ± 10	15	10,20
	1.5	23 ± 12	35 ± 14	13	6,20
	2.0	20 ± 8	31 ± 4	12‡	5,18
Block at 1 min (%)	0.75	67 ± 3	62 ± 31	−5	−29,19
	1.5	83 ± 8	81 ± 19	−3	−17,11
	2.0	91 ± 5	94 ± 8	3	−3,9
Maximum block (%)	0.75	69 ± 15	94 ± 4	24	14,34
	1.5	86 ± 7	97 ± 4	10	5,15
	2.0	91 ± 5	99 ± 1	8	4,12
Onset time (s)	0.75	62 ± 16	126 ± 33	64	48,81
	1.5	62 ± 13	96 ± 20	33	18,47
	2.0	52 ± 14	82 ± 21	30	15.46

Values are mean ± SD.

* Value assessed at adductor pollicis minus the one assessed at the larynx.

† In case zero is not within the 95% confidence interval, the difference is considered to be statistically significant different from zero.

‡ n = 9.

ORG 9487 was calculated using a cumulative dose technique, and patients with complete block were included in the determination of the dose–response curve. This method overestimates the ED_{90} of the short or intermediate duration of action neuromuscular relaxants.[10] Concerning the laryngeal adductor muscles, our results suggest that the ED_{90} at these muscles is close to 2 mg/kg. This suggest a high dose-to-response ratio for ORG 9487 between the laryngeal adductor muscles and the adductor pollicis. This sparing effect at the vocal cords has

Table 3. Recovery Characteristics

Time of Recovery	Dose (mg·kg⁻¹)	Larynx	Adductor Pollicis	Estimated Mean Difference*	95% Confidence Interval†
REC 25 (min)	0.75	2.4 ± 0.5	5.6 ± 0.9	3.8‡	3.1, 4.5
	1.5	3.7 ± 2.2	10.2 ± 2.5	6.5	4.7, 8.3
	2.0	7.4 ± 3.6	13.9 ± 2.6	6.6	3.7, 9.4
REC 75 (min)	0.75	5.5 ± 2.0	11.3 ± 1.8	6.0§	4.4, 7.5
	1.5	9.7 ± 3.7	18.3 ± 5.2	8.4	4.9, 11.9
	2.0	16.7 ± 4.3	25.0 ± 4.3	8.2	3.3, 13.2
Recovery index	0.75	5.1 ± 1.6	5.6 ± 1.3	1.0¶	−2.8, 4.7
	1.5	6.1 ± 1.8	8.1 ± 2.8	1.9	−0.1, 3.9
	2.0	9.4 ± 1.9	11.1 ± 2.8	1.7	−1.5, 4.8
REC of TOF = 70%	0.75	—	17.9 ± 2.9		
	1.5	—	30.4 ± 10.1		
	2.0	—	40.5 ± 5.1		

Values are mean ± SD.

TOF = train-of-four.

* Value assessed at adductor pollicis minus the one assessed at the larynx.

† In case zero is not within the 95% confidence interval, the difference is considered to be statistically significant different from zero.

‡ n = 4.

§ n = 9.

¶ n = 3.

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been demonstrated after administration of vecuronium,[3] rocuronium,[4] and mivacurium.[11] The reasons for the resistance of the laryngeal adductor muscles to nondepolarizing muscle relaxants have been discussed already.[4] The main hypothesis concerns the role of muscle fiber types. The muscles involved in closure of the glottis (*i.e.*, the thyroarytenoid muscle) have fast contraction times,[12] whereas the adductor pollicis is composed mainly of slow fibers.[13] The density of acetylcholine receptors is greater in the fast than in the slow contraction fibers.[14] It is likely that more receptors need to be occupied to block a fast muscle than a slow muscle.

The onset time of ORG 9487 at both muscles is rapid. This may be a result of the agent's low potency.[15] Although the doses of nondepolarizing muscle relaxants were not exactly equipotent, onset time at the laryngeal adductor muscles is 3.3 ± 0.2 min, 1.4 ± 0.3 min, and 1 ± 0.2 min after administration of 0.07 mg/kg vecuronium,[3] 0.5 mg/kg rocuronium,[4] and 1.5 mg/kg ORG 9487, respectively. Onset times of 1.5 mg/kg ORG 9487 at the laryngeal adductors muscles is close to that observed with 0.5 mg/kg succinylcholine.[5] The more rapid onset at the vocal cords than at the adductor pollicis muscle suggests a more rapid equilibration between plasma concentration and those at the airway muscles when compared with the adductor pollicis muscles. Plaud *et al.*[16] recently reported for rocuronium that the half-life of k_e0 was significantly shorter at the laryngeal adductor muscles (2.7 ± 0.6 min) than at the adductor pollicis (4.4 ± 1.5 min).

The onset time at the adductor pollicis muscle decreased significantly when the dosage was increased, whereas the onset at the laryngeal adductor muscles did not significantly decrease. The lack of differences in the onset time at the laryngeal adductor muscles could be explained by the incomplete block of these muscles. The limiting factors of the onset of action at the laryngeal muscles for drugs of low potency such as ORG 9487 might be the time required for the drug to reach the neuromuscular junction.[16] Onset time less than 1 min could be difficult to achieve because its take at least 50 s before drug can reached the capillaries near the neuromuscular junction.[17] Compared with 0.5 mg/kg succinylcholine,[5] the duration of action of ORG 9487 is longer at the larynx and the adductor pollicis. At the larynx, 25% recovery and the 75% recovery were achieved in 2.1 min and 3.7 min after 0.5 mg/kg succinylcholine instead of 7.4 min and 16.7 min after 2 mg/kg ORG 9487. At the adductor pollicis, these recovery

times were 3.1 min and 4.5 min after 0.5 mg/kg succinylcholine and 13.9 min and 25 min after 2 mg/kg ORG 9487. However, ORG 9487 has a shorter duration of action at the adductor pollicis and the laryngeal adductor muscles when compared with other nondepolarizing muscle relaxants.[3,4] This may be a result of the rapid redistribution of ORG 9487,[18] the rate of recovery from neuromuscular block being mainly governed by the rate of the plasma concentration decay.

The recovery index increased significantly with dosage. Two mechanisms may explain this phenomenon. The administration of larger doses of ORG 9487 shifts the period of recovery of neuromuscular block to a phase characterized by a slower decay of plasma concentration because of a decreased contribution of the distribution process.[18] The contribution of the blocking effect of the 3-OH metabolite has been demonstrated after 1 h of infusion-induced neuromuscular block.[18] However, it is unlikely that the 3-OH metabolite may play a role after a single bolus dose only because it is less potent than ORG 9487 (at least in the cat) and its concentration remains low.[18]

In summary, ORG 9487 is a new neuromuscular blocking agent with a rapid onset of action, especially at the vocal cords. Onset and duration of action are faster at the vocal cords than at the adductor pollicis muscle. However, laryngeal muscles resist the effect of ORG 9487, so complete block was not attained with the highest dosage tested (2 mg/kg). Further studies are required to compare ORG 9487 and succinylcholine in clinical conditions and to determine if ORG 9487 is an acceptable alternative to succinylcholine for rapid-sequence induction of anesthesia.

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