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The Neuromuscular Effects of ORG9426 in Patients Receiving Balanced Anesthesia

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In searching for a nondepolarizing muscle relaxant with intermediate duration but more rapid onset of action than the presently available compounds, the neuromuscular and circulatory effects of ORG9426 were investigated in two studies in humans receiving fentanyl, droperidol, thiopental, and nitrous oxide–oxygen anesthesia. Eighty patients, randomly assigned to one of four groups of 20 each, received 0.12, 0.16, 0.20, or 0.24 mg/kg ORG9426. In the first study, the doses (in milligrams per kilogram) of ORG9426 that caused 50% (ED_{50}), 90% (ED_{90}), or 95% (ED_{95}) neuromuscular block were determined by the individual dose-response method; they were 0.170, 0.268, and 0.305 mg/kg, respectively. In the second study, after induction of anesthesia, patients received 0.6 mg/kg (about $2 \times ED_{95}$) of ORG9426, either in a single bolus (group 1) or in two unequal (0.1 and 0.5 mg/kg) increments 4 min apart (group 2). After the administration of 0.6 mg/kg ORG9426, maximal neuromuscular block developed in 1.5 ± 0.12 min in group 1 and in 1.2 ± 0.14 min in group 2. Patients tracheas were intubated after development of the maximal neuromuscular effect of the intubating dose and after the recording of heart rate and systolic and diastolic blood pressure. There was no difference in the clinical duration of the intubating doses, which were 40.0 ± 3.2 (15–73) min in group 1 and 39.3 ± 2.4 (19–57) min in group 2. Clinical duration of the first repeat dose of 0.1, 0.15, or 0.2 mg/kg ORG9426, administered whenever the twitch tension elicited by the first train-of-four impulse recovered to 25% of control were 11.0 ± 1.0 (4–16), 18.3 ± 1.6 (7–50), and 28.1 ± 6.3 (7–69) min, respectively. The recovery index was 16.7 ± 1.2 (4–64) min. In 89 patients residual neuromuscular block at the end of anesthesia could be antagonized with 0.5 mg/kg edrophonium + 0.015 mg/kg atropine in 2 to 5 min. No circulatory or other side effects attributable to ORG9426 and no signs or symptoms of recurrent paralysis were observed in the postanesthetic recovery room. The onset time of ORG9426 was shorter than those of other nondepolarizing muscle relaxants previously studied in identically anesthetized patients. "Priming" did not shorten the onset time of $2 \times ED_{95}$ ORG9426. Because of its rapid onset of action, of the currently available nondepolarizing muscle relaxants, ORG9426 may prove useful for facilitating rapid sequence intubation. (Key words: Neuromuscular relaxants, ORG9426: pharmacodynamics.)

THE INTRODUCTION OF VECURONIUM and other nondepolarizing muscle relaxants of intermediate duration of action into clinical practice represents a significant advance for the provision of safe and controllable muscular relaxation. Slow onset of action, however, has been a common shortcoming of all of these agents. It has been reported that in cats the onset time of ORG9426, the 2-morpholino-16-allyl-pyrrolidino derivative of the 3-hydroxy analog of vecuronium (figure 1), was shorter, its duration of action similar, and its neuromuscular potency about one fifth that of vecuronium.[1] Like vecuronium, the cardiovascular effects of ORG9426 were insignificant. It was the purpose of this study to determine whether ORG9426 has similar desirable neuromuscular properties in anesthetized humans.

The effects of ORG9426 were observed in two studies in patients anesthetized with fentanyl, droperidol, thiopental, and nitrous oxide in oxygen ("balanced anesthesia"). In the first study, referred to as the "single-dose-response study," the doses (in milligrams per kilogram) of ORG9426 that caused 50% (ED_{50}), 90% (ED_{90}), or 95% (ED_{95}) neuromuscular block were determined. In the second study, referred to as the "clinical study," the neuromuscular and circulatory effects of the $2 \times ED_{95}$ dose, administered in a single bolus or in two unequal increments (by the "priming principle"),[2,3] were observed.

Materials and Methods

ASA physical status 1, 2, and 3 patients of both sexes, between 18 and 66 yr of age, gave informed consents to participate in two studies approved by the institutional review board of the hospital. Patients who had neuromuscular disorders, those who received drugs in the perioperative period that could effect neuromuscular activity, and women with child-bearing potential were excluded from these studies.

Anesthetic Management

All patients were given, intramuscularly, 50–100 mg diphenhydramine hydrochloride and 50–100 mg meperidine hydrochloride 60–90 min before induction of anesthesia. Anesthesia was induced with 0.5–1 μg/kg fentanyl citrate, 0.1 mg/kg droperidol, and 2–3 mg/kg thiopental sodium, all injected intravenously (iv), and 4 l/min nitrous oxide–2 l/min oxygen. After induction of anesthesia, an oropharyngeal airway was inserted, and ventilation was manually assisted or controlled, *via* face mask, until tracheal intubation. Anesthesia was maintained with a 2-l/

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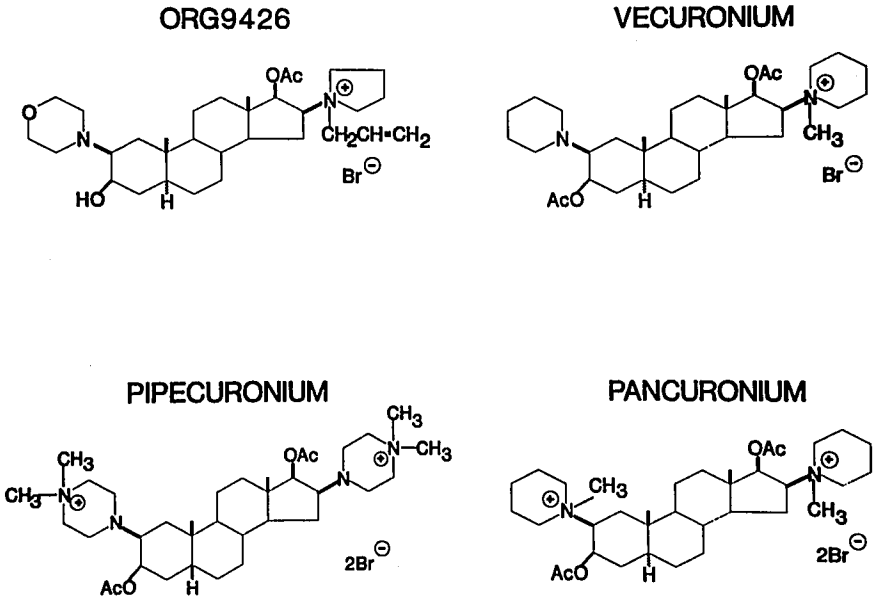

FIG. 1. Structural formulas of ORG9426, vecuronium, pancuronium and pipecuronium. Note that the first two are monoquaternary and that the second two are bisquaternary compounds.

min nitrous oxide–1-l/min oxygen gas mixture, 25–100-μg increments of fentanyl, and, occasionally, 25–100 mg thiopental.

MONITORING OF NEUROMUSCULAR TRANSMISSION

Neuromuscular transmission was monitored in both the dose-response and clinical studies by continuous recording of the force of contraction of the adductor pollicis muscle, elicited by stimulation of the ulnar nerve at the wrist, and was quantitated by a force displacement transducer (Myotrace® model APM-6, Professional Instruments). Trains of four (TOF), supramaximal, square-wave impulses of 0.2-ms duration at 2 Hz, were administered every 12 s. In both studies 4 min was allowed for stabilization of the response to TOF stimulation before administration of the first dose of ORG9426.

End-tidal carbon dioxide tension was maintained at near 40 mmHg throughout anesthesia. Rectal temperature was between 35 and 37° C. No effort was made to measure the surface temperature of the thenar.

DETERMINATION OF THE DOSE-RESPONSE

The individual dose method was used for the determination of the dose response of ORG9426. To find the optimal dose range, after induction of anesthesia, three patients each were injected iv, in an ascending order, with 0.12, 0.16, 0.20, or 0.24 mg/kg ORG9426. The data obtained in these 12 patients were not used for the determination of the dose response. Subsequently, four groups of 20 patients each received randomly one of the above four doses of ORG9426.

Since in our clinical experience, in adults, the neuromuscular effect of muscle relaxants is more closely related to body surface area (BSA) than to body weight (BW),[4] correction was made for deviations of BW from the 70-kg "reference man"[5] with the empirical formula:

$$\text{Corrected BW } (BW_C)\ (kg) = 0.5 \times BW\ (kg) + 35\ kg$$

The BW_C obtained with this simple formula was very similar to that obtained using the equation of DuBois and DuBois:[6]

$$BSA\ (m^2) = BW\ (kg)^{0.425} \times \text{height}\ (cm)^{0.725} \times 71.84$$

or the appropriate nomogram based on it. The BSA of the "reference man" of 70-kg BW and 170-cm height determined with this formula is 1.81 m^2. This means that the BW corresponding to 1 m^2 BSA of the reference man equals 70/1.81 = 38.68 kg. Accordingly, the BW_C (in kilograms) can be calculated by determining the BSA (in meters squared) from the DuBois–DuBois nomogram and multiplying it by 38.68. The BW_C of 40 patients of the clinical study determined with the proposed simple formula and the DuBois–DuBois equation had a correlation coefficient 0.97 ($y = 1.09 \times -7.03$).

After development of the maximal effect of the initial dose, the total dose of ORG9426 administered was increased to 0.3 mg/kg by the injection of a variable (0.06–0.18 mg/kg) second dose. If after the second dose the twitch tension elicited by the first impulse of TOF (T1) was more than 10% of control, then greater than 90% neuromuscular block was achieved by the injection of one or, occasionally, two 0.1-mg/kg increments of ORG9426. At this time the trachea was intubated.

The ED_{50}, ED_{90}, and ED_{95} mg/kg doses of ORG9426 were determined with the log-dose–probit method. Data from 73 patients in whom the injected dose of ORG9426 caused 1–99% block were used for the calculation of the

TABLE 1. Demographic Data

Study	Number of Patients	Age (yr)	Weight (kg)	Sex	
				Male	Female
Dose-response	80	48.0 ± 1.4 (18–66)	80.1 ± 1.6 (54.5–122.7)	53	27
Clinical					
Group 1	20	44.3 ± 2.9 (21–62)	80.2 ± 3.9 (53.6–122.5)	13	7
Group 2	20	46.6 ± 2.8 (22–64)	74.2 ± 36 (48.2–104.5)	14	6

Data for age and weight are mean ± SEM; range in parentheses.

dose response. Data from 7 patients in whom the initial dose of ORG9426 did not decrease T1 or increased it above control were not included in the calculation of the dose response. If muscular relaxation had to be prolonged, 0.10 or 0.15 mg/kg ORG9426 was administered whenever T1 increased to 25% of control.

CLINICAL STUDIES

In the clinical studies, 40 patients were randomly divided into two groups of 20 each. Four to 5 min after induction of anesthesia, patients in group 1 were given iv a single 0.6-mg/kg dose (about 2 × ED_{95}) of ORG9426. At the same time, those in group 2 received an 0.1 mg/kg priming dose of ORG9426 followed by an 0.5 mg/kg "intubating" dose 4 min later. This time interval was selected to allow for the development of the maximal neuromuscular effect of the priming dose. After development of the maximal neuromuscular effect of the intubating dose, the patients' tracheas were intubated. The maximal neuromuscular effect, the time from end of injection of intubating dose to the development of the maximal effect (onset time), and the time required for the return of T1 to 25% of control (clinical duration) were recorded. When T1 returned to 25% of control after the administration of the intubating dose, patients in both clinical groups, who required continued muscular relaxation, received a 0.15- or 0.20-mg/kg increment of ORG9426. The same doses were repeated, whenever T1 returned to 25% of control, for as long as muscular relaxation was required.

In both studies, whenever possible, recovery of neuromuscular transmission was allowed to proceed spontaneously, and the recovery index (the time from 25 to 75% recovery of T1) and the time for 10–90% recovery of T1 were recorded. In 89 patients in whom the ratio of the fourth to first response to TOF (T4/T1 ratio) was less than 0.75 at the end of surgery, the residual neuromuscular block was antagonized with a mixture of 0.5 mg/kg edrophonium and 0.015 mg/kg atropine, injected over 60 s. T1 and the T4/T1 ratio were measured before and at 2 and 5 min after the end of administration of the antagonist.

Heart rate and systolic and diastolic blood pressure were determined automatically with a Dinamap® apparatus (model 1846SX1P) at 1-min intervals during the first 30 min of anesthesia and every 3 min thereafter. In addition, in the second study a triggered determination of these variables was initiated just before the injection of the 2 × ED_{95} dose of ORG9426, after development of its maximal neuromuscular effect, and just before and at 2 and 5 min after the end of injection of the antagonist. Arterial hemoglobin oxygen saturation and end-expiratory carbon dioxide tension were measured throughout induction and maintenance of anesthesia.

STATISTICS

The statistical significance of the differences of the various parameters were determined by analysis of variance followed by Tukey's test[7] or by Student's *t* test, for paired or unpaired variables, as indicated. $P < 0.05$ was considered significant.

Results

The demographic data of the patients who participated in our dose-response and clinical studies, summarized in

TABLE 2. The Neuromuscular Effects of Increasing Doses of ORG9426 in Patients Receiving Balanced Anesthesia

Dose (mg/kg)	T1 (% of control)	T4/T1 Ratio	Onset Time (min
0.12	82.2 ± 4.4 (55.0–114.8)	0.50 ± 0.04 (0.23–0.78)	3.8 ± 0.2 (2.4–7.0)
0.16	65.7 ± 6.2 (7.4–100)	0.34 ± 0.04 (0.00–0.60)	3.9 ± 0.1 (3.0–5.0)
0.20	36.7 ± 5.4 (8.3–103.8)	0.12 ± 0.04 (0.00–0.63)	4.2 ± 0.2 (3.0–5.0)
0.24	18.1 ± 2.8 (2.3–46.7)	0.06 ± 0.02 (0.00–0.43)	4.4 ± 0.2 (3.0–6.2)

Data are mean ± SEM of 20 observations; range in parentheses.

Onset time is time from end of injection to development of maximal effect.

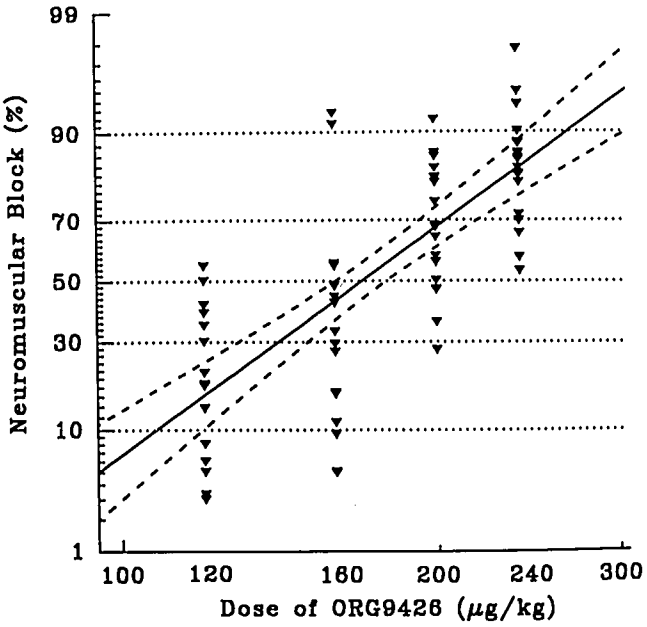

FIG. 2. The log-dose–probit response regression line of the neuromuscular effect of ORG9426. Broken lines indicate 95% confidence limits.

table 1, indicate that with regard to age, BW, and sex, the patient population of the dose-response and the clinical studies are similar.

The mean ± standard error of the neuromuscular effect, expressed as percent of control T1, of the T4/T1 ratio, and of the time for the development of the maximal effect of the various doses of ORG9426, are summarized in table 2. The data indicate that, as with other muscle relaxants,[8,9] there is considerable individual variation in the neuromuscular effect of the same milligram-per-kilogram dose of ORG9426.

The ED_{50}, ED_{90}, and ED_{95} of ORG9426, determined from the log-dose–probit response regression line obtained in 73 patients (see Materials and Methods) (fig. 2) were 0.170, 0.268, and 0.305 mg/kg, respectively.

The duration of action of repeat doses of ORG9426, the recovery index, the time for spontaneous recovery of T1 from 10 to 90% of control, and the effect of edrophonium on the residual neuromuscular block in the dose-response and clinical studies were similar. Therefore the observations made on these variables in the two studies are presented together.

In group 2 the priming dose of 0.1 mg/kg ORG9426 decreased T1 to 88.0 ± 4.6% of control and T4/T1 to 0.58 ± 0.04.

The neuromuscular effects of intubating doses of ORG9426, summarized in table 3, indicate that the time for development of 80% depression of T1, onset time, and clinical duration were similar in the two groups. Intubating conditions in group 1 were excellent (vocal cords motionless and no bucking) in all patients; in group 2 they were excellent in 16 and good (slight bucking) in 4 patients.

The clinical duration of the first repeat doses of 0.10, 0.15, and 0.20 mg/kg ORG9426 were 11.0 ± 1.0 (n = 11, 4–16), 18.3 ± 1.6 (n = 28, 7–50), and 28.1 ± 6.3 (n = 10, 7–69) min, respectively. On repeated administration of the same dose of ORG9426 to the same patients there was a tendency for a moderate increase in the clinical duration of successive doses (table 4).

The data presented in table 5 indicate that there is considerable individual variation in the spontaneous recovery parameters of ORG9426.

Of the 120 patients, neuromuscular transmission recovered spontaneously in 31 who required no muscular relaxation after intubation. Of the 89 patients who received edrophonium, recovery parameters could not be measured in 4 patients because of mechanical difficulties. In the remaining 85, the residual neuromuscular block at the end of anesthesia could be antagonized readily, in 2–5 min, by 0.5 mg/kg edrophonium and 0.015 mg/kg atropine (table 6). In 9, however, the T4/T1 ratio at 5 min after edrophonium ranged from 0.50 to 0.73. These patients were given oxygen by mask and were discharged to the postanesthetic recovery room only when clinical signs (*e.g.*, head lift sustained for more than 5 s and grip strength) indicated adequate recovery of neuromuscular transmission.

There were no significant changes in heart rate or systolic and diastolic blood pressure, measured at 1-min in-

TABLE 3. Neuromuscular Effects of Intubating Doses of ORG9426

Variables	Group 1 (n = 20)	Group 2 (n = 20)
Time to 80% block (min)	0.90 ± 0.05 (0.5–1.4)	0.86 ± 0.07 (0.4–1.8)
Onset time (min)	1.49 ± 0.12 (0.7–3.0)	1.23 ± 0.14 (0.6–3.5)
Maximal effect	Complete block in 38 of 40 patients*	
Clinical duration (min)	40.0 ± 3.2 (15–73)	39.3 ± 2.4 (19–57)

Data are mean ± SEM; range in parentheses.

Group 1 received a single, 0.6 mg/kg iv dose. Group 2, received 0.1 and 0.5 mg/kg iv doses 4 min apart. Onset time is time from end of injection to development of maximal depression of T1; clinical duration is time from end of injection of intubating dose to recovery of T1 to 25% of control.

* Neuromuscular block was 97.4% in one patient in group 1 and 92.9% in another in group 2.

TABLE 4. Clinical Duration (min) of Repeat Doses of ORG9426

Dose	Repeat Doses (mg/kg)		
	0.1	0.15	0.20
First	10.5 ± 1.2 (9) [4–16]	15.4 ± 1.5 (16) [7–30]	17.7 ± 3.0 (6) [7–29]
Second	13.4 ± 0.8 (9) [10–18]	18.3 ± 1.5 (16) [10–32]	22.8 ± 5.4 (6) [7–47]
Third	13.8 ± 1.2 (9) [6–20]	20.0 ± 1.9 (16) [12–38]	27.7 ± 8.4 (6) [8–68]

Data are mean ± SEM of number of observations indicated in parentheses; range in brackets.

Repeat doses were administered whenever T1 recovered to 25% of control. Observations were made of patiens who received at least three doses.

* Significantly different ($P < 0.05$; paired t test) from duration of first dose.

tervals, from the start of injection of 0.5 or 0.6 mg/kg ORG9426 to the development of its maximal neuromuscular effect.

Discussion

Comparison of the findings of this study with other studies conducted by us earlier on identically premedicated and anesthetized patients indicate that in humans, ORG9426 is less potent than vecuronium[10] or pipecuronium[10] (table 7). However, after iv administration of its 2 × ED_{95} dose, the onset time of ORG9426, 1.5 ± 0.1 min, is less than that of vecuronium,[10] pipecuronium,[10] or pancuronium[10] (table 7). The administration of ORG9426 in divided doses decreased neither onset time nor the time to development of 80% neuromuscular block. This indicates that under our experimental conditions (*i.e.*, with our priming dose and time interval), priming with ORG9426, in contrast to the situation with vecuronium,[2,3] does not decrease onset time.

Currently there is no definite explanation for the unusually rapid onset of the neuromuscular effect of ORG9426. It has been suggested[11] that because of the relatively large intubating dose of ORG9426, the diffusion gradient from plasma to pre- and postsynaptic receptor sites at the neuromuscular junction is greater than that with other, more potent, muscle relaxants. Another possible explanation is that the plasma protein binding of ORG9426 is less than that of pancuronium (88%) or vecuronium (91%).[12]

TABLE 5. Spontaneous Recovery From ORG9426-induced Neuromuscular Block

Variable	n	Mean ± SEM (Range)
Recovery index	69	16.7 ± 1.2 (4–64)
T4/T1 ratio at 75% recovery of T1	68	0.40 ± 0.02 (0.13–0.73)
Time (min) from 10% to 90% recovery of T1	37	24.4 ± 2.0 (7–56)
T4/T1 ratio at 90% recovery of T1	45	0.52 ± 0.03 (0.20–0.79)

Recovery index is the time (min) for recovery of T1 from 25% to 75% of control.

Onset times suitable for "rapid-sequence intubation" can be achieved by the iv administration of 0.6 mg/kg[13] succinylcholine in 1.6 ± 0.1 min or by 6 × ED_{95} (0.3 mg/kg) or 8 × ED_{95} (0.4 mg/kg) vecuronium in 1.5 ± 0.1 min or 1.3 ± 0.1 min,[14] respectively, or by the administration of 0.065[3] or 0.1 mg/kg[15] vecuronium in divided doses in 1.6 ± 0.2 and 1.4 ± 0.1 min, respectively. Succinylcholine, however, has many potentially dangerous side effects.[16] Large (6–8 × ED_{95}) single doses of vecuronium cause unpredictable, excessive prolongation (up to 215 min)[17] of the clinical duration of the neuromuscular block and occasional difficulties in the reversal of the block at the end of anesthesia,¶ and the administration of vecuronium in divided doses prolongs induction time. In contrast, after the administration of 2 × ED_{95} ORG9426, onset times, suitable for facilitation of rapid-sequence intubation can be achieved just as rapidly as with the above mentioned techniques, without excessively long clinical duration, prolongation of the induction time, or unwanted side effects.

Little information is available on the pharmacokinetics of ORG9426. The elimination half-life, 203 ± 169 min (mean ± standard deviation), distribution volume at steady state, 283 ± 183 ml/kg, and plasma clearance, 2.8 ± 0.9 ml/kg/min, in six patients with normal kidney function and in five patients with renal failure were similar.[18] There were no significant differences between the above kinetic parameters of ORG9426 and those of vecuronium determined in the same laboratory in four patients.[19] The mean elimination half-life of ORG9426 (203 min) was about 2.5 times longer than that of vecuronium (79.5 min) reported earlier,[19] but their difference, probably because of the small number of observations and the large standard deviation, was not significant.

In conclusion, ORG9426 has a short onset time; the clinical duration of its intubating dose is intermediate; and it appears to have no circulatory side effects. Because of these desirable properties, of the currently available nondepolarizing muscle relaxants, ORG9426 may prove

¶ Unpublished observations, 1988.

TABLE 6. Antagonism of the Residual ORG9426 Block

	T1	T4/T1
Before edrophonium	60.7 ± 2.8 (11–106)	0.33 ± 0.02 (0–0.73)
After edrophonium		
2 min	99.2 ± 2.3 (50–161)	0.83 ± 0.01 (0.47–1.00)
5 min	104.3 ± 2.2 (50–164)	0.86 ± 0.01 (0.50–1.00)

Data are mean ± SEM of 85 cases; range in parentheses.

TABLE 7. Comparison of the Neuromuscular Effect of ORG9426, Vecuronium, Pipecuronium, and Pancruonium in Patients Receiving Anesthesia

Compound	ORG9426	Vecuronium	Pipecuronium	Pancuronium
ED_{50} (mg/kg)	0.170	0.030	0.020	0.033
ED_{90} (mg/kg)	0.268	0.044	0.033	0.049
Relative potency	1.0	6.1	8.1	5.5
Onset time (min)	1.5 ± 0.1	5.9 ± 1.0	3.6 ± 0.4	3.7 ± 0.5
Clinical duration (min)	40.0 ± 3.2	36.3 ± 2.1	110.5 ± 0.3	115.8 ± 8.1
Recovery index (min)	16.6 ± 1.1	14.3 ± 1.4	44.5 ± 8.2	41.3 ± 4.2

ED_{50} and ED_{90} of pancuronium from Donlon *et al.*;[20] all other data on vecuronium, pipecuronium, and pancuronium from Foldes *et al.*[10] Relative potency is at the ED_{95} level; onset time is time to the development of maximal effct of 2 × ED_{95} doses of ORG9426 (0.6 mg/kg), vecuronium (0.1 mg/kg), pipecuronium (0.08 mg/kg), or pancuronium (0.1 mg/kg).

to be the agent of choice for the facilitation of rapid-sequence intubation.

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