Duration of Action of Supplemental Doses of Vecuronium is Related to the Duration after the Initial Dose

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Vecuronium was administered in an initial dose of $0.1 \sim 0.3$ mg·kg^{-1} and in supplemental doses of 0.03 mg·kg^{-1} or 0.05 mg·kg^{-1} in 74 patients (ASA class 1 or 2) scheduled for abdominal surgery. The duration of the neuromuscular blockade provided by vecuronium after both the initial and supplemental doses was determined using the evoked integrated electromyographic device. A statistically significant positive correlation (correlation coefficient: $0.83 \sim 0.91$) was found between the duration of action of the initial dose and that of the first to fourth supplemental doses.

The regression lines of each of the first four supplemental doses to the initial dose were very similar to each other. These results suggest that, since the duration of action of supplemental doses of vecuronium was prolonged in patients showing a long duration of action of the initial dose, it would be wise to avoid blind adherence to a predetermined schedule for supplemental administration. Rather, anesthesiologists should take into account the patient's response to the initial dose and then decide the most appropriate timing for supplemental doses. Moreover, since vecuronium shows little cumulative effect even after 4 supplemental administrations in clinical-range doses, it can be concluded that vecuronium can be safely used in a wide dose range. (Key words: vecuronium, duration of action, initial dose, supplemental dose)

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Vecuronium exerts no significant effects on the cardiovascular system, and it also causes little release of histamine[1-2]. In addition, the duration of the neuromuscular blocking action of vecuronium is comparatively short,

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and there is little or no cumulative effect[3]. Recently, since the administration of a large dose accelerates the onset of its action and prolongs the duration of that action, vecuronium has been tested by administration in a large initial dose to patients scheduled to undergo surgical procedures expected to last 3 or more hours[4-6]. However, as with all drugs, individual patient variability exists in the response to drug administration, and this tendency may become more ap-

parent as the dosage increases. Although vecuronium shows little or no cumulative effects, it can be imagined that recovery from its neuromuscular blockade might be slower than expected and prolonged apnea might occur if vecuronium were administered in a large initial dose followed by repeated supplemental doses.

In this study, the authors investigated the relationship between the duration of action after the initial dose of vecuronium and the duration of action after supplemental doses of this neuromuscular blocking agent.

Methods

The subjects of this study were 74 adult patients scheduled to undergo abdominal surgery and with ASA class 1 or 2. Patients with neuromuscular or metabolic diseases were excluded. Each patient was given a full explanation of the methods and objectives of this clinical study, and informed consent was received from each patient prior to inclusion in this study. Taking into account the duration of operation decided by the surgeons, the patients were assigned to 5 groups on the basis of the initial dose of vecuronium: Group I, 0.1 $mg \cdot kg^{-1}$; Group II, 0.15 $mg \cdot kg^{-1}$; Group III, 0.2 $mg \cdot kg^{-1}$; Group IV, 0.25 $mg \cdot kg^{-1}$; and Group V, 0.3 $mg \cdot kg^{-1}$. The supplemental dose of vecuronium was 0.03 $mg \cdot kg^{-1}$ for Group I, and 0.05 $mg \cdot kg^{-1}$ for each of Groups II $\sim$ V.

All patients were premedicated with either atropine or scopolamine, and most of the patients were also administered petidine hydrochloride at approximately 1 $mg \cdot kg^{-1}$. After the patient was transferred to the operating room, the ECG was monitored, and the heart rate and blood pressure were measured every 5 min. An electromyographic device (Relaxograph, Helsinki, Finland) was employed to monitor the state of neuromuscular blockade.

The stimulating surface electrode was placed over the ulnar nerve in the forearm, while the comparative electrode was placed over the center of the wrist joint and the measuring electrode was taped to the corresponding adductor pollicis muscle. The control value was determined either when the patient was awake or when the patient went to sleep after an intravenous injection of 100 mg of thiopental. Thereafter, anesthesia was induced with thiopental at 4 $\sim$ 5 $mg \cdot kg^{-1}$, and the initial dose of vecuronium was administered as a bolus intravenous injection. Controlled ventilation was carried out using 100% oxygen, and tracheal intubation was performed at the time of maximum blockade or when T_1 reached 0. During the operation, anesthesia was maintained with oxygen (3 $l \cdot min^{-1}$), nitrous oxide (3 $l \cdot min^{-1}$) and 1.0 $\sim$ 2.5% enflurane, and the Pa_{CO_2} was maintained at 35 $\sim$ 45 mmHg.

The first amplitude (T_1) of the train-of-four (TOF) stimulation was used as the parameter for the neuromuscular blockade. The duration of the neuromuscular blocking action was defined as the time from the administration of vecuronium until the time when the value of T_1 recovered to 25% of the control value. When a supplemental dose was needed, the previously decided dose of vecuronium was administered at the time when the value of T_1 recovered to 25% of the control value. After the surgery was completed, in principle, 1 mg of atropine sulfate and 2 mg of neostigmine were administered at the time when the value of T_1 recovered to 25% of the control value.

The measured values were expressed as the mean $\pm$ S.D. The background factors of the study population were examined by analysis of variance. The correlation between the duration of action of the initial dose and each of the first to fourth supplemental doses

Table 1. Characteristics of patients

Group	Initial dose $(mg \cdot kg^{-1})$	Supple-mental dose $(mg \cdot kg^{-1})$	Number of patients			Age (yr)	Height (cm)	Body weight (kg)	Body surface area: BSA (m^2)
			F	M	total				
I	0.1	0.03	12	7	19	50 ± 14	$157 - 6$	53 ± 6	1.51 ± 0.1
II	0.15	0.05	8	7	15	53 ± 14	$157 - 8$	53 ± 6	1.51 ± 0.1
III	0.2	0.05	6	6	12	55 ± 14	156 ± 11	53 ± 10	1.51 ± 0.2
IV	0.25	0.05	8	6	14	51 ± 15	157 ± 7	55 ± 11	1.54 ± 0.2
V	0.3	0.05	7	7	14	61 ± 11	154 ± 10	53 ± 10	1.49 ± 0.2

Mean $\pm$ S.D. No significant differences were found between any groups.

Table 2. Number of patients receiving each supplemental dose

Group	Initial dose	Supplemental dose			
		1st	2nd	3rd	4th
I	19	18	17	13	10
II	15	14	8	5	3
III	12	11	9	7	3
IV	14	13	7	6	3
V	14	9	8	4	0
Total	74	65	49	35	19

was analyzed from the regression line obtained by the least squares method. For all analyses, a *P* value of less than 0.05 was regarded as statistically significant.

Results

No statistically significant differences were found between any of the treatment groups in terms of the number of patients, sex ratio, age, height, body weight or body surface area (BSA) (table 1). The duration of action after the initial administration of vecuronium [Y (min)] showed a first-order linear correlation in relation to the initial dose [X $(mg \cdot kg^{-1})$], with $Y=498X - 14.5$ (n=74, r=0.72, *P* < 0.01). A statistically significant positive correlation was thus found between these two parameters. At least 3 supplemental doses were administered to subjects in each of the five treatment groups. None of the subjects in

Group V received a 4th supplemental dose. Analyses were not performed for 5 or more supplemental doses since the number of administered subjects was 2 or less in all except Group I (table 2).

The relationships between the duration of action of the supplemental dose [Y (min)] and the duration of action of the initial dose [X (min)] were as follows.

For the 1st supplemental dose:
$$Y=9.56+0.523X$$
(n=65, r=0.910, *P* < 0.01) [fig. 1]

For the 2nd supplemental dose:
$$Y=9.57+0.559X$$
(n=49, r=0.891, *P* < 0.01) [fig. 2]

For the 3rd supplemental dose:
$$Y=16.7+0.413X$$
(n=35, r=0.831, *P* < 0.01) [fig. 3]

For the 4th supplemental dose:
$$Y=11.8+0.502X$$
(n=19, r=0.878, *P* < 0.01) [fig. 4]

A significant correlation was thus found for each supplemental dose of vecuronium and the initial dose. None of the subjects in this clinical study experienced prolonged postoperative apnea, and there were also no instances of tachycardia, bradycardia, marked decrease in the blood pressure, or ECG abnormalities.
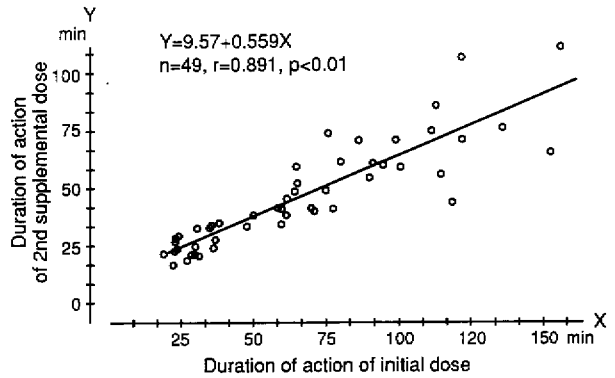
Discussion

The distribution rate constants of vecuronium are 3 times larger than those of pancuronium, while vecuronium's elimination rate constants are
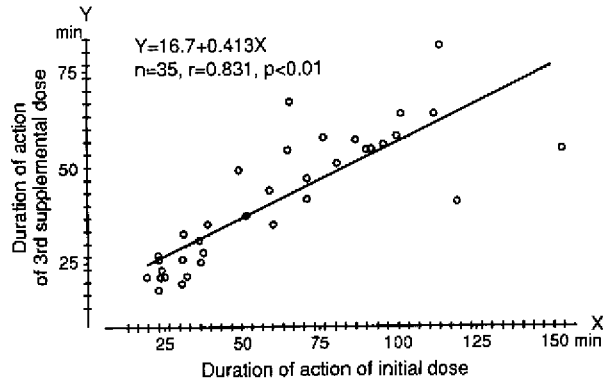
**Fig. 1.** Relationship of the duration of action between initial dose and 1st supplemental dose.
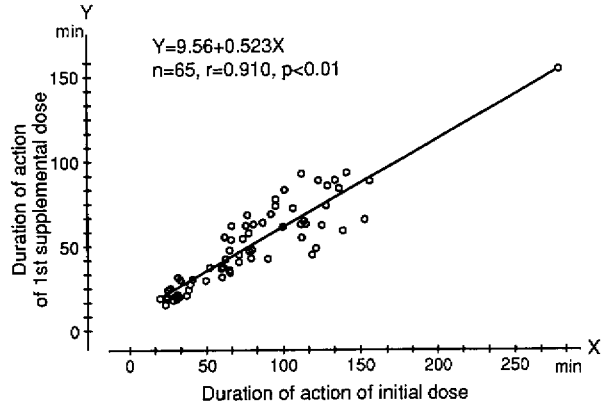
Fig. 2. Relationship of the duration of action between initial dose and 2nd supplemental dose.

Fig. 3. Relationship of the duration of action between initial dose and 3rd supplemental dose.

Fig. 4. Relationship of the duration of action between initial dose and 4th supplemental dose.
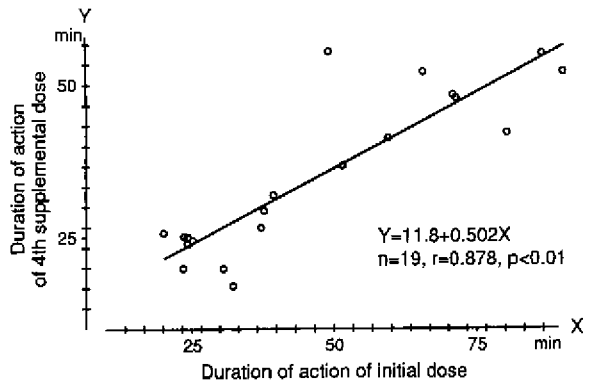
5 times larger than those of pancuronium. As a result, the disappearance of vecuronium from the blood is more rapid, and its duration of action is shorter than that of pancuronium[7]. In addition, since 70% of the administered dose of vecuronium is excreted via the liver, this drug can be relatively safely employed even in patients with renal dysfunction. However, it has been reported that the remaining approximately 30% of the administered dose is excreted in the urine as either unchanged vecuronium or as 3-deacetyl-vecuronium (3-OH metabolite)[8]. The 3-OH metabolite reportedly contains approximately 50 ~ 70% of the neuromuscular blocking action of vecuronium[9], and thus it can be imagined that the neuromuscular blocking action would be prolonged due to that activity in patients with renal dysfunction. Moreover, Hunter et al.[10] reported that, whereas the duration of action of vecuronium in cirrhotic patients did not differ from that in healthy humans up to a dosage of 0.15 mg·kg^{-1}, it was clearly prolonged with a dosage of 0.2 mg·kg^{-1}. The recovery from the neuromuscular blocking action of vecuronium will be delayed in patients with renal or hepatic dysfunction. In general, the response to muscle relaxants differs among individuals[11], and a patient's response to these drugs also varies as a function of his/her age[12], the presence/absence of a regular-use drug, and his/her general physical condition at the time of administration[13]. In the clinical settings, if it is possible to predict the duration of action of a supplemental dose of vecuronium from the patient's response to the initial dose, it might be helpful in deciding the timing for administration of the supplemental doses and in preventing the occurrence of delayed apnea.

In the present study, the authors administered initial doses of vecuronium in the range of 0.1 to 0.3 mg·kg^{-1}, and the supplemental doses were 0.05 mg·kg^{-1} in most of the patients. The supplemental dose may be considered the upper limit of the clinically-employed range, but this high dose appears to be more useful than a low dose for investigating accumulation of the drug in the body.

On the other hand, the usual initial dose is 0.1 ~ 0.15 mg·kg^{-1} and higher doses of 0.2 ~ 0.3 mg·kg^{-1} are seldom used in elderly patients. The dose response relationship cannot be truely evaluated if there is a bias in the make up of the patients in the high and low dose groups. In the present study there were no significant differences in the patient profile between the groups with regard to the number of patients, male and female ratio, age etc. This would mean that the dose response analysis of the 74 patients is applicable to a majority of the clinical cases.

With regard to the correlation between the duration of action of the initial dose of vecuronium and that of the supplemental doses, our data showed strong positive correlation coefficients of r=0.83 or higher for each of the 1st through 4th supplemental doses. These results proved that, for patients showing a long duration of neuromuscular blockade after the initial dose of vecuronium, it's action was also prolonged after the administration of supplemental doses. The duration of action of the initial dose was within 150 min except for one case which showed a remarkably long duration of 270 min. With initial doses in the range of 0.1 ~ 0.3 mg·kg^{-1}, the regression lines obtained after each of the 1st through 4th supplemental doses were very similar (fig. 5). These results indicate that, with the exception of one case showing a very prolonged duration of action after the initial dose, the duration of action even after the 4th supplemental dose is rarely pro-
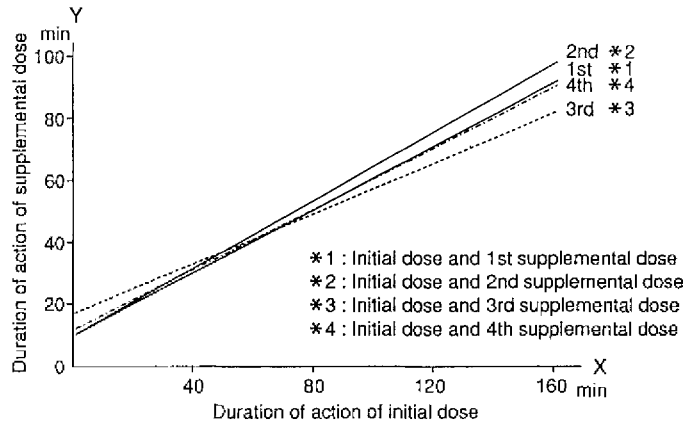
Fig. 5. Relationship of the duration of action between initial dose and each supplemental dose.

longed to a very great extent, and there is almost no accumulation of vecuronium's action in patients.

In conclusion, the duration of action of vecuronium after supplemental doses is linearly related to the duration of action after the initial dose. Therefore, anesthesiologists should avoid blind adherence to a predetermined schedule for supplemental administration and should design an appropriate supplemental administration regimen (i.e., the size of the supplemental doses and the timing of their administration) for each individual patient by giving careful consideration to the patient's response to the initial dose of vecuronium.

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