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Refining the Priming Principle for Vecuronium during Rapid-sequence Induction of Anesthesia

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Administration of a subparalyzing dose of a nondepolarizing muscle relaxant (priming dose) prior to its intubating dose hastens the onset time (time from muscle relaxant administration to 100% depression of twitch tension) of neuromuscular blockade. This study was undertaken to determine the optimal priming and intubating doses and time interval between these doses (priming interval) of vecuronium during rapid-sequence induction of anesthesia. The authors measured single-twitch tension in 79 healthy, awake, premedicated (fentanyl, 50–150 μ iv, and/or diazepam, 5–10 mg iv) patients. In Part A of the study, the priming dose was varied (0.0, 0.005, 0.01, 0.0015, or 0.02 mg/kg iv). Decrement of twitch tension and symptoms were recorded 3 min later. Four minutes after the priming dose, thiopental, 4–6 mg/kg iv, and vecuronium, 0.1 mg/kg iv, were given. Onset times for the 0.01, 0.015, and 0.02 mg/kg groups were significantly shorter than for 0.005 and 0.0 mg/kg groups. No breathing difficulties were encountered in any of the groups. Decrement of twitch tension greater than 25% of control only occurred in the 0.02 mg/kg group (4 of 11 patients). In Part B, the priming interval was varied (2, 4, or 6 min) after giving the optimal priming dose (0.01 mg/kg). Anesthesia was induced as in Part A. Onset times for the 4-min group were significantly faster than the 2- or 6-min groups. In Part C, the intubating dose was varied (0.07, 0.1, or 0.15 mg/kg iv) after the optimal priming dose and optimal priming interval (4 min). Onset times for the 0.1 mg/kg and 0.15 mg/kg groups were significantly faster than the 0.07 mg/kg group. Intubating conditions were not evaluated. The authors conclude that when vecuronium is used for rapid establishment of neuromuscular blockade during induction of anesthesia, 0.01 mg/kg iv should be given 4 min prior to 0.1 mg/kg iv. (Key words: Anesthetic techniques: rapid sequence, priming principle. Neuromuscular relaxants: vecuronium.)

ALTHOUGH VECURONIUM CAN BE given to facilitate endotracheal intubation, its relatively slow onset time (time from muscle relaxant administration to 100% depression of twitch tension) limits its usefulness in a rapid-sequence induction of anesthesia.[1] The onset time can be hastened by the administration of a subparalyzing dose of vecuronium prior to its intubating dose.[2] This has been termed "the priming principle."[2] Other investigators have shown that this principle also applies to other nondepolarizing muscle relaxants, *e.g.*, atracurium[3] and pancuronium.[4,5]

This study was undertaken to identify an optimal priming dose (the smallest dose producing the fewest symptoms and yielding the fastest onset time of twitch depression), priming interval (the shortest time from the priming dose to the intubating dose resulting in the fastest onset time of twitch depression), and intubating dose (the smallest dose producing the fastest onset time of twitch depression) of vecuronium to perform a rapid-sequence induction of anesthesia.

Methods

We obtained informed consent from patients and approval from our local Committee on Human Research to study 79 ASA I or II adult elective surgical patients. Patients were premedicated with morphine sulfate, 10 mg im, and diazepam, 10 mg po, 1 h prior to surgery. Fentanyl, 50–150 μg iv, and/or diazepam, 5–10 mg iv, was administered as necessary to facilitate awake neuromuscular monitoring in the operating room. One-half milliliter of 1% lidocaine was injected intradermally over the ulnar nerve at the wrist and two thin-walled, steel-needle, 27-gauge electrodes were placed 1 cm apart in these skin wheals. Neuromuscular function was monitored by measuring force-of-thumb adduction using a Grass FT10® force displacement (150–300 g resting tension) transducer in response to supramaximal single twitch (0.15 Hz) stimulation of the ulnar nerve at the wrist.

The study was divided into three parts (table 1). In Part A, we determined the optimal priming dose. Once baseline twitch recording was stable, a priming dose of vecuronium, consisting of 0.0, 0.005, 0.01, 0.015, or 0.02 mg/kg iv, was given. Decrement of twitch tension and the presence or absence of five symptoms/side effects were noted 3 min after the administration of the priming dose. Patients were asked to open their eyes, to protrude their tongue, and to indicate if they had blurred vision, difficulty breathing, or trouble swallowing. Four minutes after the priming dose, anesthesia was induced with thiopental, 4 mg/kg iv bolus, followed immediately by vecuronium, 0.1 mg/kg iv bolus. Additional thiopental, 2 mg/kg iv, was given 30 s prior to intubation. Intubation was performed after 100% depression of twitch tension. Intubating conditions were not evaluated. The priming interval (4 min) and intubating dose (0.1 mg/kg) were arbitrarily chosen in this part of the study.

Onset times (times from administration of the intubating dose of vecuronium to 80 and 100% depression of twitch tension) were measured. Onset times were compared using analysis of variance and Student Newman-Keuls Test.[6] Incidences of symptoms from the priming dose were compared among priming dose groups using chi-square analysis. The optimal priming dose was selected from this part of the study and used in Parts B and C.

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TABLE 1. Priming Doses, Priming Intervals, and Intubating Doses

Part	Group	Priming Dose (mg/kg)	Priming Interval (min)	Intubating Dose (mg/kg)
A	1 (n = 10)	0	4	0.1
	2 (n = 10)	0.005	4	0.1
	3 (n = 11)	0.01	4	0.1
	4 (n = 11)	0.015	4	0.1
	5 (n = 10)	0.02	4	0.1
B	6 (n = 6)	0.01	2	0.1
	7 (n = 7)	0.01	6	0.1
C	8 (n = 6)	0.01	4	0.07
	9 (n = 8)	0.01	4	0.15

The optimal priming interval in Part B was studied. Patients were premedicated and neuromuscular function was monitored as in Part A. Once baseline twitch recording was stable, the optimal priming dose of vecuronium was given intravenously. Two, 4, or 6 min later, anesthesia was induced in the same manner as in Part A. Onset times of the three groups were compared statistically and the optimal priming interval was selected.

In Part C, the optimal intubating dose of vecuronium was studied. Patients were premedicated and monitored as in previous parts. After stable twitch height, the optimal priming dose was given. Following the optimal priming interval, anesthesia was induced with thiopental, 4–6 mg/kg iv, and vecuronium, 0.07, 0.10, or 0.15 mg/kg iv. Onset times were compared as before to determine the optimal intubating dose.

Results

A priming dose of 0.01 mg/kg (fig. 1), with a priming interval of 4 min (fig. 2), and an intubating dose of 0.1 mg/kg (fig. 3) was the combination that produced the most rapid onset of neuromuscular blockade and the fewest side effects from the priming dose (table 2).

In Part A, onset times for the five priming doses (0.0, 0.005, 0.01, 0.015, or 0.02 mg/kg) were 174 ± 65, 158 ± 60, 102 ± 76, 113 ± 48, and 110 ± 22 s (mean ± SD),

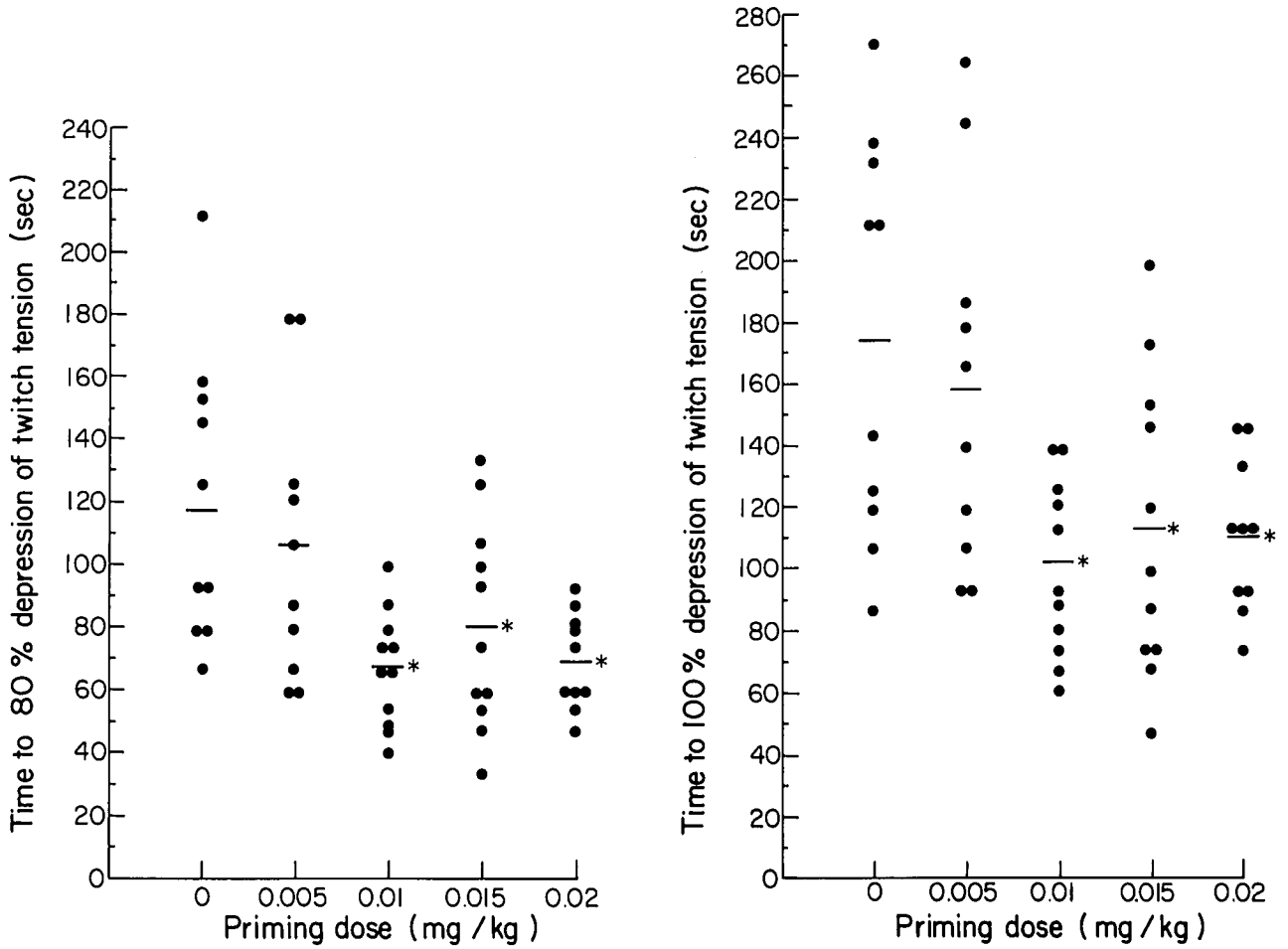

FIG. 1. Onset times to 80% (*A*) and 100% (*B*) depression of twitch tension *versus* priming doses of vecuronium. (—) indicates the mean for the groups. Circles represent individual patients. * indicates significant difference from 0.0 and 0.005 mg/kg groups ($P < 0.05$).

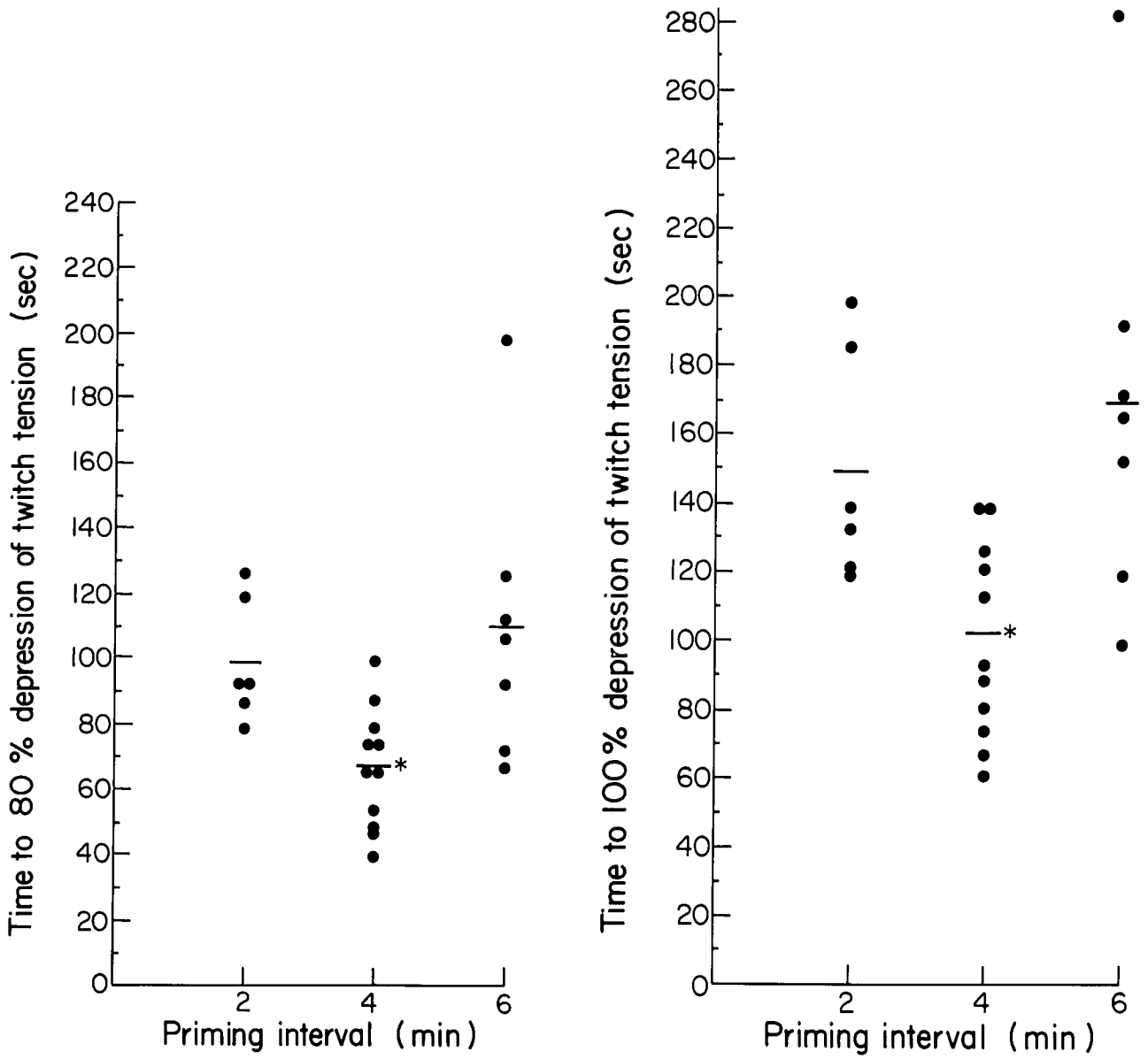

FIG. 2. Onset times to 80% (*A*) and 100% (*B*) depression of twitch tension *versus* priming intervals after a priming dose of vecuronium, 0.01 mg/kg. (—) indicates mean for the groups. Circles represent individual patients. * indicates significant difference ($P < 0.05$).

respectively. The 0.01, 0.015, and 0.02 mg/kg groups had significantly shorter onset times than the 0.0 and 0.005 mg/kg groups ($P < 0.05$). However, there was no difference between the 0.01, 0.015, and 0.02 mg/kg groups ($P > 0.05$). Some patients in the 0.005 mg/kg group had a rapid onset of paralysis (fig. 1). The largest priming dose (0.02 mg/kg) group had the greatest number of side effects, symptoms ($P < 0.05$), and the greatest decrement of twitch tension at 3 min (table 2). Blurred vision was the most common side effect encountered in all groups that received a priming dose, and no patient complained of breathing difficulties. For subsequent parts of the study, vecuronium, 0.01 mg/kg iv, was selected as the optimal priming dose.

In Part B, the priming interval of 4 min allowed the fastest onset time (102 ± 26 s), compared to the 2-min (148 ± 34 s) and 6-min (169 ± 60 s) priming intervals ($P < 0.05$) (fig. 2). Twitch tension decrement from 0.01 mg/kg priming dose was negligible for all priming intervals.

In Part C, intubating doses of 0.1 and 0.15 mg/kg allowed faster onset of paralysis (102 ± 26 and 114 ± 35 s, respectively) than 0.07 mg/kg (196 ± 23 s) (fig. 3) ($P < 0.05$). However, there was no difference in onset time between 0.1 and 0.15 mg/kg ($P > 0.05$).

Discussion

We determined an acceptable combination of priming dose, priming interval, and intubating dose for vecuro-

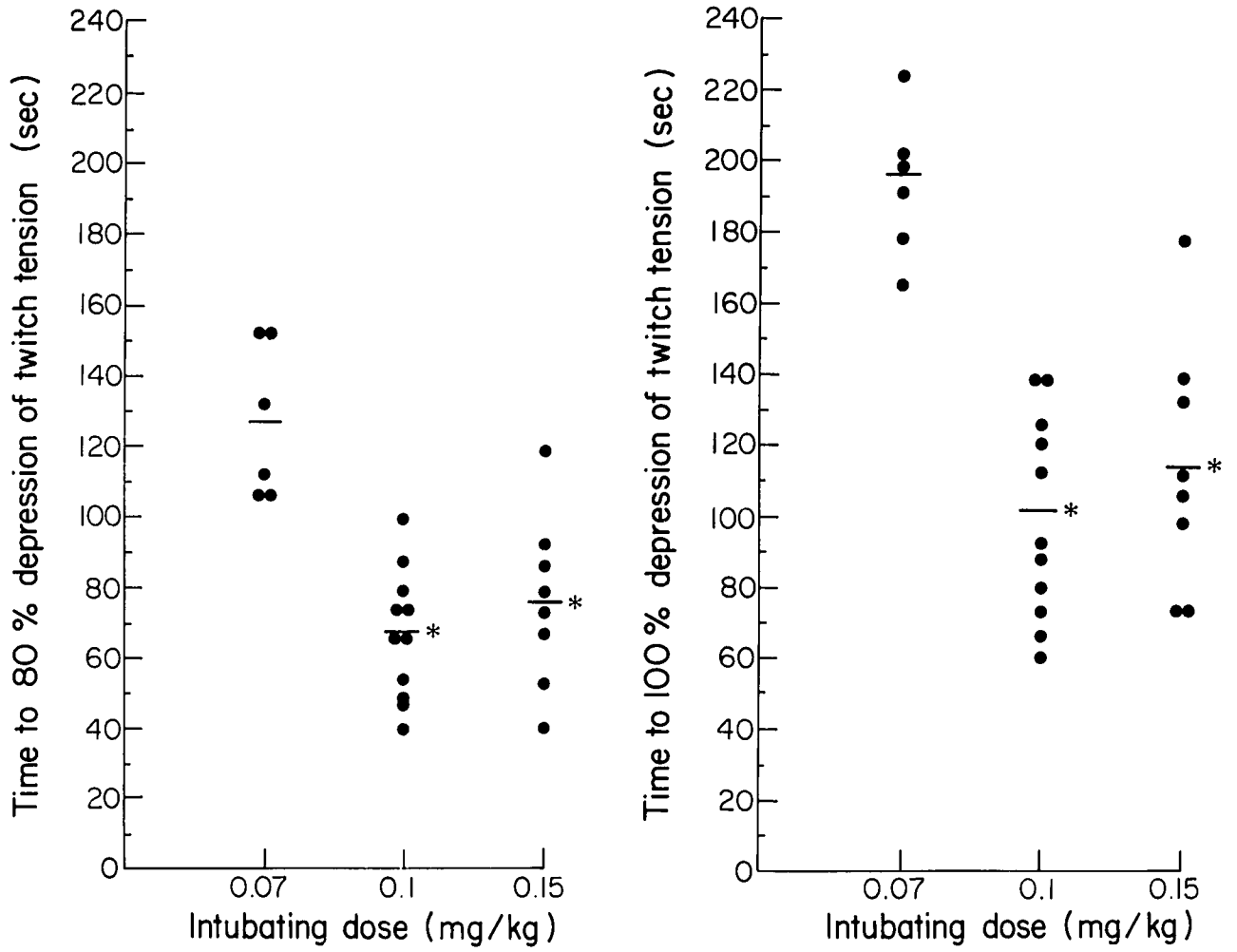

FIG. 3. Onset times to 80% (*A*) and 100% (*B*) depression of twitch tension *versus* intubating doses of vecuronium after a priming dose of vecuronium, 0.01 mg/kg, followed by a priming interval of 4 min. (—) indicates the mean for the groups. Circles represent individual patients. * indicates significant difference from 0.07 mg/kg group ($P < 0.05$).

TABLE 2. Incidence of Side Effects or Symptoms 3 Min after Different Priming Doses of Vecuronium

	Priming Dose (mg/kg)			
Side Effects/Symptoms	0.005 n = 10	0.01 n = 11	0.015 n = 11	0.02 n = 11
Blurred vision	2*	5	9	10
Unable to protrude tongue	0	0	0	6*
Unable to open eyes	0	1	4	9*
Difficulty swallowing	0	1	1	10*
Difficulty breathing	0	0	0	0
Decrement of twitch tension				
0%	10	10	11	5
0–25%	0	1	0	2
25–50%	0	0	0	2
>50%	0	0	0	2

Values are number of patients having symptoms.
* Different from other groups, $P < 0.05$.

nium that produces the fastest onset time with the fewest side effects and symptoms when compared to other combinations tested. Schwarz *et al.*,[2] Gergis *et al.*,[3] and Nagashima *et al.*[7] demonstrated a faster onset of action of nondepolarizing muscle relaxant when a priming dose was used. However, these investigators did not vary the priming dose, interval, and intubating dose to determine the optimal priming combination in awake patients. Schwarz *et al.*[2] administered a 0.015 mg/kg priming dose to awake patients, followed by a 0.05 mg/kg intubating dose, but they did not measure onset time or quantitate side effects. None of the studies examined potential side effects and symptoms from the priming dose.

The components of an ideal priming combination are the priming dose, the priming interval, and the intubating dose. As the priming dose of vecuronium is decreased from 0.01 mg/kg, the onset time of neuromuscular blockade from the intubating dose is the same as if no

priming dose is administered. The minimum priming dose of vecuronium to achieve a reliably faster onset of action is 0.01 mg/kg. A few patients achieve neuromuscular blockade rapidly with a lower priming dose (0.005 mg/kg) than 0.01 mg/kg (fig. 1). However, this effect is inconsistent. As the priming dose is increased from 0.01 mg/kg, neuromuscular blockade is not additionally hastened, but side effects and symptoms are increased. For these reasons, 0.01 mg/kg appears to be the optimal priming dose of the doses examined in this study.

The priming interval also appears to influence the onset of neuromuscular blockade. By shortening the vecuronium priming interval from 4 to 2 min, the onset time of the intubating dose is prolonged. In this case, it is possible that not enough time is allowed for the priming dose to reach the appropriate receptors. If a priming interval longer than 4 min is used, the onset time of the intubating dose also is prolonged. In this case, redistribution or elimination of the priming dose may be occurring. It is not surprising that 4 min was the optimal priming interval in this study. Onset time as measured in this study is a result of two doses of vecuronium superimposed on each other: a subparalytic dose (a dose producing less than 100% depression of twitch tension) or priming dose and an intubating dose. The onset time for a vecuronium subparalytic dose is approximately 6 min.[8] The fastest onset time for intubating doses of vecuronium is about 2 min.[1] Thus, both doses are obtaining their peak effect simultaneously if the priming interval is 4 min.

No difference in onset time was found between vecuronium intubating doses of 0.1 mg/kg and 0.15 mg/kg. An intubating dose larger than 0.15 mg/kg of vecuronium may further shorten onset time. However, as the dose of vecuronium is increased, the duration of action is prolonged. For example, Fahey *et al.*[1] demonstrated that as the intubating dose of vecuronium is increased from 0.07 to 0.28 mg/kg, duration of action is prolonged from 34 ± 8 to 174 ± 12 min (mean ± SEM), respectively. Thus, with larger intubating doses, one of the most important features of vecuronium, its intermediate duration of action, is lost. For this reason, we recommend that 0.10 mg/kg of vecuronium should be used as the intubating dose.

A different combination of priming dose, priming interval, and intubating dose may achieve onset times as fast as those obtained with our recommended combination. For example, a smaller priming dose (*e.g.*, 0.005 mg/kg) combined with a larger intubating dose (*e.g.*, 0.2 mg/kg) might achieve a fast neuromuscular blockade. However, the intubating dose would probably cause a longer duration of action in this case. On the other hand, if we had combined a larger priming dose (*e.g.*, 0.02 mg/kg) with a smaller intubating dose (*e.g.*, 0.07 mg/kg), onset time may have been as fast or faster than the one obtained in this study. However, side effects and symptoms from this priming dose might be considered unacceptable. Because we determined the optimal priming dose, interval, and intubating dose in a sequential manner, we did not examine all possible combinations of these variables.

In this study, we demonstrated that neuromuscular blockade can be obtained faster when a nondepolarizing muscle relaxant is preceded by a subparalyzing dose of the same nondepolarizing muscle relaxant. We also showed that an appropriate combination of the priming dose, priming interval, and intubating dose is necessary to optimize this effect. Therefore, when rapid establishment of neuromuscular blockade with vecuronium is desired, we recommend the administration of vecuronium, 0.01 mg/kg, for priming dose followed by a priming interval of 4 min, and an intubating dose of vecuronium, 0.1 mg/kg. This technique may be the method of choice when succinylcholine is contraindicated or undesirable (*e.g.*, potential hyperkalemic response,[9] increased intraocular pressure,[10] increased intragastric pressure,[11] or malignant hyperthermia[12]) and when rapid facilitation of endotracheal intubation is needed.

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