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Onset of vecuronium-induced neuromuscular block after a long priming interval

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Abstract
Purpose. We examined whether a new application of the priming principle, i.e., having the priming dose of vecuronium administered before the insertion of the epidural catheter, would hasten the onset of the neuromuscular block induced by the intubating dose of vecuronium.
Methods. Forty-five adult female patients scheduled for general anesthesia combined with epidural anesthesia were studied. In group A ($n = 15$), the priming dose of vecuronium, 0.01 mg·kg^{-1}, was administered before insertion of the epidural catheter. The intubating dose of vecuronium, 0.09 mg·kg^{-1}, was given after the insertion of the epidural catheter. In group B ($n = 15$), the priming dose of vecuronium, 0.01 mg·kg^{-1}, was given 4 min before the intubating dose of vecuronium, 0.09 mg·kg^{-1}. In the control group ($n = 15$), no priming dose was given, and only the intubating dose of vecuronium, 0.10 mg·kg^{-1}, was administered. In all three groups, general anesthesia was induced with propofol 2.5 mg·kg^{-1}, and the trachea was intubated when T1/control value (control twitch height in response to train-of-four stimuli) was less than 0.1.
Results. In group A, the priming dose was given 16 ± 3 min (mean ± SD) before the administration of the intubating dose. The times to onset of neuromuscular block in groups A and B, and the control group were: 145 ± 30, 184 ± 45, and 219 ± 23 s, respectively ($P < 0.05$ among the three groups). In all three groups, intubating conditions (graded on a four-point scale) were excellent ($P = 0.59$). Before the induction of anesthesia, symptoms of paralysis were observed in 5, 4, and 0 patients in groups A and B and the control group, respectively ($P < 0.05$ between group A or B *vs* control group).
Conclusions. If the priming dose of vecuronium is given after a long priming interval (16 ± 3 min), the time to onset of the neuromuscular block caused by the intubating dose of vecuronium is markedly shorter than when the conventional priming interval of 4 min is employed.

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Key words Vecuronium · Onset of neuromuscular block · Priming principle · Train-of-four

Introduction

The administration of a subparalyzing dose of a nondepolarizing neuromuscular relaxant prior to the injection of the intubating dose, the so-called "priming principle", has been studied for many years. If the subparalyzing dose is given prior to the intubating dose, the onset of neuromuscular block caused by the intubating dose can be hastened [1,2]. However, the "priming interval" i.e., the interval from the administration of the priming dose to that of the intubating dose should be several minutes. This priming interval interferes with the speedy induction of general anesthesia, and so the priming principle is not necessarily of clinical use. Toboada et al. [1] reported that the best priming interval and the best priming dose of vecuronium were 4 min and 0.01 mg·kg^{-1}, respectively. Nevertheless, Rupp et al. [3] showed that the time to onset of neuromuscular block for a subparalyzing dose of vecuronium was approximately 6 min. We hypothesized that if the priming interval were to be more than 6 min, the onset of neuromuscular block caused by the intubating dose of vecuronium might be still more hastened. In addition, especially in patients undergoing general anesthesia combined with epidural anesthesia, if the priming dose is given before the insertion of the epidural catheter, the priming interval just before the induction of general anesthesia can be used effectively. Although some symptoms of paralysis may occur [1,2], the administration of the subparalyzing dose of vecuronium prior to the insertion of the epidural catheter would be useful to hasten the onset of neuromuscular block. We studied the time to the onset of neuromuscular block, the presence of symptoms of paralysis, and the intubating

conditions, when the priming dose was given before the insertion of the epidural catheter, as compared with findings when the priming dose was administered 4 min before the injection of the intubating dose and the findings when no priming dose was given.

Patients and methods

We studied 45 adult female patients, ASA physical status I–II, scheduled for elective gynecological surgery under general anesthesia combined with epidural anesthesia. None of the patients had neuromuscular, hepatic, renal, metabolic, or cardiac disease, or was taking any drugs known to affect the action of neuromuscular relaxants. Additional exclusion criteria involved the possibility of difficult direct laryngoscopy (i.e., Mallampati class ≧ III, obesity, massive jaw, facial burns, disproportionately increased size of tongue, decreased mandibular space, and decreased mobility of airway joints). Written informed consent was obtained from each subject, and the institutional Human Investigation Committee approved the protocol of this study. The patients were allocated randomly to three groups, of 15 patients each: groups A and B, and the control group.

Premedication, consisting of atropine 0.01 $mg \cdot kg^{-1}$ and hydroxyzine 1 $mg \cdot kg^{-1}$ was administered intramuscularly 30 min before the induction of anesthesia in each group.

In group A, the priming dose of vecuronium, 0.01 $mg \cdot kg^{-1}$, was given intravenously before insertion of the epidural catheter. After they had received the priming dose of vecuronium, the patients were settled in a lateral position. The epidural catheter was inserted using an 18-gauge Tuohy needle (Perifix Mini Set, B. Braun, Tokyo, Japan) at L1-2 or L2-3, and a test dose of 1% lidocaine 2 ml was injected through the epidural catheter. The patients were asked to inform the medical staff immediately of any intolerable symptoms of paralysis; for example, difficulty in breathing. If the patients reported any such symptoms, or if arterial hemoglobin oxygen saturation (SpO_2) decreased below 90% during the insertion of the epidural catheter, we stopped the insertion of the epidural catheter at once and induced general anesthesia. Once insertion of the epidural catheter was completed, the patients were settled in a supine position. Subsequently, on one forearm of the patient, two surface electrodes were positioned over the ulnar nerve at the wrist. A force transducer was attached to the thumb of the investigated arm. Thumb preload was adjusted to 250 g. Anesthesia was induced with propofol 2.5 $mg \cdot kg^{-1}$. After loss of eyelash reflex was confirmed, train-of-four (TOF) stimuli were applied every 15 s, at 50 mA, using a nerve stimulator (Isolator; Nihon-Kohden, Tokyo, Japan), via the surface electrodes. The corresponding responses of the adduction of the thumb to the TOF stimuli were quantified, using a neuromuscular transmission analyzer (Myograph 2000; Biometer, Odense, Denmark), and recorded on a paper chart at a chart speed of 1 $mm \cdot s^{-1}$. For the TOF stimuli, four single-twitch stimuli, consisting of a square-wave of 0.2 ms-duration, were delivered every 0.5 s. The height of T1 (first response in the TOF) was regarded as the control twitch height. After the recording of the control twitch height, the intubating dose of vecuronium, 0.09 $mg \cdot kg^{-1}$, was administered intravenously. The time interval from the administration of propofol to the intubating dose of vecuronium, 0.09 $mg \cdot kg^{-1}$, was set at 90 s.

In group B, the epidural catheter was inserted in the same manner as in group A. However, the priming dose of vecuronium was not given before the insertion of the epidural catheter. After the epidural catheter was inserted, the force transducer was attached to the thumb of the investigated arm. The priming dose of vecuronium, 0.01 $mg \cdot kg^{-1}$, was then given intravenously. Propofol 2.5 $mg \cdot kg^{-1}$ was administered intravenously 150 s after the injection of the priming dose of vecuronium, and, after the loss of the eyelash reflex, the control twitch height was recorded. Ninety seconds after the propofol injection, the intubating dose of vecuronium, 0.09 $mg \cdot kg^{-1}$, was administered intravenously. In this way, the priming interval, i.e., the interval from the priming dose to the intubating dose, was settled at 4 min.

In the control group, the insertion of the epidural catheter and the attachment of the force transducer were performed in the same way as in groups A and B. No priming dose was given. Anesthesia was induced with propofol 2.5 $mg \cdot kg^{-1}$, intravenously, and, after the loss of the eyelash reflex, the control twitch height was recorded. The intubating dose of vecuronium, 0.10 $mg \cdot kg^{-1}$, was then given intravenously. In the control group, the time interval from the administration of propofol to the intubating dose of vecuronium, 0.09 $mg \cdot kg^{-1}$, was settled at 90 s.

In each group, the insertion of the epidural catheter and administration of vecuronium or propofol were performed by an experienced anesthetist (Y.S.). Immediately after the injection of the intubating dose of vecuronium, another experienced anesthetist (K.K.), who was not aware of the time point of the administration of the priming or the intubating dose of vecuronium, the depth of the neuromuscular block, or the purpose of this study, entered the operating room, and ventilated the lungs with oxygen, 6 $l \cdot min^{-1}$, administered using a face mask. The anesthetist (Y.S.) asked the other anesthetist (K.K.) to open the mouth of the patient, using his fingers, and to insert a laryngoscope

when the T1/control value decreased to 0.2 or less, and to intubate the trachea when the T1/control value was 0.1 or less. When tracheal intubation was performed, an A no. 3 or no. 4 Macintosh laryngoscope and a cuffed 7.5-mm internal diameter (ID) tracheal tube (Murphy High Volume Low Pressure; Fuji Systems, Tokyo, Japan) were used.

In the three groups, the times from the administration of the intubating dose to the start of laryngoscopy, to the tracheal intubation, and to the T1/control value of 0 (onset time) were determined. In addition, the TOF ratio (T4/T1) just before the administration of the intubating dose, the presence or absence of symptoms of paralysis (heavy eyelids, blurring of vision, difficulty in breathing, difficulty in swallowing, difficulty in lifting the head, and general discomfort) before the injection of propofol, and the intubating conditions were investigated. The intubating conditions were graded using a scoring method reported previously [4], which took three factors, jaw relaxation, condition of the vocal cords, and response to tracheal intubation, into consideration. The three factors were scored on a four-point scale (0–3). Total scores of 8–9, 6–7, 3–5, and 0–2 were considered excellent, good, fair, and poor, respectively.

The peripheral skin temperature over the adductor pollicis muscle of the investigated hand was monitored using a peripheral skin thermometer (Terumo-Finer, CTM-303; Terumo, Tokyo, Japan).

The patient characteristics, time of onset of neuromuscular block, and the TOF ratio just before the administration of the intubating dose were compared among the three groups, using analysis of variance (ANOVA) and Tukey's multiple comparison. Comparisons of the numbers of patients in whom any symptoms of paralysis were observed and comparisons of the intubating conditions were made among the three groups, using the χ^2 test. $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed using a statistical package (SYSTAT 8.0; SPSS, Chicago, IL, USA).

Results

The clinical characteristics of the three groups of patients did not differ significantly (Table 1).

No patients in any of the three groups voluntarily reported any intolerable symptoms of paralysis during the insertion of the epidural catheter. SpO_2 did not fall below 90% in any of the patients. We did not need to stop the insertion of the epidural catheter in any patient and the epidural catheter was inserted uneventfully in all patients.

As shown in Table 2, time to the start of laryngoscopy, time to tracheal intubation, and time to the onset of neuromuscular block in group A were all shorter than these times in group B and the control group ($P < 0.05$), and these times were shorter in group B than in the control group ($P < 0.05$).

The TOF ratio measured just before the administration of the intubating dose did not differ significantly among the three groups (0.96 ± 0.09, 0.99 ± 0.02, and 1.00 ± 0.02 in groups A and B and the control group, respectively; mean ± SD, *P*, Not significant). In 13 patients in group A, the TOF ratios just before the intubating dose were above 0.9. In the two remaining patients in group A, the TOF ratios just before the intubating dose were low, at 0.71 and 0.79. In contrast,

Table 1. Characteristics of patients in the three groups

	Group A	Group B	Control group
Number of patients	15	15	15
Age (years)	52 ± 8	48 ± 9	54 ± 6
Height (cm)	155 ± 7	158 ± 9	157 ± 6
Weight (kg)	55 ± 6	57 ± 7	56 ± 7
Mallampati class I/II	13/2	13/2	12/3

Numbers of patients and age, height, and weight did not differ significantly among the three groups
Values are numbers or means ± SD
Group A, Priming interval, 16 ± 3 min; group B, priming interval, 4 min; control group, no priming dose given

Table 2. Times from administration of the intubating dose to the start of laryngoscopy (T1/control ≦ 0.2), to tracheal intubation (T1/control ≦ 0.1), and to the onset of neuromuscular block (T1/control = 0) in the three groups

	Group A	Group B	Control group
Time to start of laryngoscopy (s)	102 ± 21*:**	130 ± 34*	167 ± 25
Time to tracheal intubation (s)	117 ± 25*:**	150 ± 40*	190 ± 26
Time to onset of NM block (s)	145 ± 30*:**	184 ± 45*	219 ± 23

* $P < 0.05$ as compared with control group; ** $P < 0.05$ as compared with group B and control group
Values are means ± SD
Groups A and B, and control group, as in Table 1 footnote. See text for explanation of T1/control
NM, Neuromuscular

Table 3. The absence or presence of symptoms of paralysis (and numbers of patients in whom any symptom of paralysis was observed) before the injection of propofol in the three groups

	A	B	Control
Number of patients in whom symptoms of paralysis were observed	5*	4*	0
Heavy eyelids	2	2	0
Blurring of vision	2	2	0
Difficulty in breathing	0	0	0
Difficulty in swallowing	1	1	0
Difficulty in lifting head	0	0	0
General discomfort	1	2	0

* $P < 0.05$ as compared with the control group
Values are numbers
Groups A and B, and control group, as in Table 1 footnote

in all the patients in group B and all these in the control group, the TOF ratios just before the intubating dose were above 0.9. No patient voluntarily complained of any intolerable symptoms of paralysis during the insertion of the epidural catheter. However, when we asked about the presence of symptoms of paralysis before the injection of propofol, patients in groups A and B more frequently complained of symptoms of paralysis than those in the control group ($P < 0.05$; Table 3). In 5 patients in group A who complained of paralysis, the TOF ratios, measured before the injection of propofol, were 1.02, 0.99, 0.95, 0.79, and 0.71 (0.89 ± 0.13; mean $\pm$ SD). In 4 patients in group B who complained of paralysis, the TOF ratios before the propofol injection were 0.99, 0.96, 0.96, and 0.94 (0.96 ± 0.02; mean $\pm$ SD).

The intubating conditions in 14 patients in group A, 15 in group B, and 14 in the control group were excellent, according to the scoring system that we used. No patient was classified as fair or poor. In no patient did the peripheral skin temperature decrease to less than 32°C.

Discussion

In our group A, the long priming interval (16 ± 3 min), during which time the epidural catheter was inserted, shortened the time to the onset of neuromuscular block, compared with the time to this onset after the conventional priming interval (of 4 min, in group B).

It has been recommended that the priming dose of vecuronium, 0.01 mg·kg^{-1}, should be given 4 min before the intubating dose [1]. However, Rupp et al. [3] reported that the time to onset of neuromuscular block for a subparalyzing dose of vecuronium was approximately 6 min. With regard to this report, it appears that the best priming interval for vecuronium may not be 4 min, but 6 min. In the clinical setting it is troublesome for anesthetists to wait for 6 min after the administration of the priming dose of vecuronium. However, in our group A, the anesthetists did not need to wait for the priming interval, because the priming dose was given before the insertion of the epidural catheter. The present study demonstrated that when no priming dose was given, the mean time to the onset of vecuronium 0.1 mg·kg^{-1}-induced neuromuscular block was 219 s. This was comparable with previous data [5,6]. In contrast, in group B, the mean time from the administration of the intubating dose of vecuronium to the onset of neuromuscular block was 184 s. Furthermore, in group A, the mean time from the injection of the intubating dose to the onset of neuromuscular block was 145 s. Thus, as compared with the time to onset of neuromuscular block when no priming dose was given, the priming dose of vecuronium given 4 min before the intubating dose, and that given before the insertion of the epidural catheter, shortened the time to onset of neuromuscular block by 35 s and by 74 s, respectively. We propose that the administration of the priming dose prior to the insertion of the epidural catheter is useful, especially for patients in whom general anesthesia combined with epidural anesthesia is scheduled.

As noted above, the time to onset of neuromuscular block for a subparalyzing dose of vecuronium is approximately 6 min [3]. We cannot explain clearly the reason why the long priming interval, i.e., 16 ± 3 min, resulted in the apparently rapid onset of neuromuscular block caused by the intubating dose of vecuronium. However, Koscielniak-Nielsen et al. [5] showed that the time to onset of neuromuscular block induced by vecuronium 0.03 mg·kg^{-1} was as long as 473 ± 30 s (mean $\pm$ SD) in adult patients aged 60–80 years. Thus, in their study, although the dose of vecuronium was higher than the priming dose, the time to onset of the neuromuscular block was approximately 8 min. Kopman et al. [7] reported that, after the administration of a subparalyzing dose of mivacurium, even if the TOF ratio recovered to 1.00, the dysfunction of the extraocular muscles did not necessarily abate. Moreover, in their study, several subjects reported that diplopia persisted for periods in excess of 1 h after the termination of the mivacurium infusion. With regard to this finding, we suggest that the neuromuscular blocking effect caused by a subparalyzing dose of a nondepolarizing neuromuscular relaxant would have lasted for a long time even after the TOF ratio recovered to 1.00. This hypothesis may explain the present finding that a long priming interval, i.e., 16 ± 3 min, resulted in a markedly rapid time to onset of vecuronium-induced neuromuscular block.

In this study, the onset of neuromuscular block was defined as the time when the T1/control value was 0.

However, in previous studies in which the time of onset of rocuronium- or mivacurium-induced neuromuscular block was investigated, the definitions of the onset time differed to some extent. Patel et al. [8], Cooper et al. [4], and Pühringer et al. [9] defined the onset of neuromuscular block as the state in which the T1/control value was 0, was minimum, and was 0.05, respectively. Only Patel et al. [8] regarded the onset of neuromuscular block as a T1/control value of 0, as in our study. They noted that the times to the onset of rocuronium 0.9 mg·kg^{-1}- and mivacurium 0.25 mg·kg^{-1}-induced neuromuscular block were 108 s and 183 s, respectively. In our study, the time to onset of neuromuscular block caused by vecuronium in group A was 145 s. Therefore, if the priming dose of vecuronium, of 0.01 mg·kg^{-1}, was given before the insertion of the epidural catheter, the time to onset of neuromuscular block caused by vecuronium 0.09 mg·kg^{-1} was longer than the time to onset of neuromuscular block caused by rocuronium, but shorter than that caused by mivacurium. Although the onset of neuromuscular block caused by rocuronium is quick, rocuronium is not available in most countries; instead, the administration of a subparalyzing dose of vecuronium before the insertion of the epidural catheter is thought to be useful to hasten the onset of neuromuscular block.

In our group A, the mean time interval from the administration of the intubating dose of vecuronium to tracheal intubation was 117 s. In groups A and B and the control group, excellent intubating conditions were obtained in 14 (93%), 15 (100%), and 14 (93%) patients, respectively. Patel et al. [8] showed that, 90 s after the administration of rocuronium 0.9 mg·kg^{-1}, intubating conditions were excellent in most patients. Maddineni et al. [10] noted that 150 s after mivacurium 0.2 mg·kg^{-1}, excellent intubating conditions were produced in only about 40% of patients. Hence, to perform tracheal intubation rapidly, the intubating condition with a priming dose of vecuronium given before the insertion of the epidural catheter, followed by the intubating dose of vecuronium, is inferior to the condition with a bolus injection of rocuronium, but would be superior to the condition with a bolus injection of mivacurium.

In our groups A and B, symptoms of paralysis, i.e., heavy eyelids, blurring of vision, difficulty in swallowing, difficulty in lifting the head, and general discomfort were demonstrated in 5 and 4 patients, respectively. Kopman et al. [7] noted that a TOF ratio of more than 0.9 ensured sufficient recovery of neuromuscular block, but in some volunteers, symptoms of paralysis could be demonstrated at a TOF ratio of more than 0.9. In fact, the present study revealed that symptoms of paralysis were observed even when the TOF ratio was above 0.9. However, in the patients who complained of such symptoms, difficulty in breathing was not observed. This is in accordance with a previous finding [1]. Martin et al. [11] showed that the priming dose of vecuronium, of 0.01 mg·kg^{-1}, did not increase the risk of acid reflux into the esophagus. In contrast, Mahajan and Laverty [12] reported that, 3 min after the administration of vecuronium 0.01 mg·kg^{-1}, lung function was impaired in healthy volunteers. Consequently, it should be taken into consideration that the priming dose of vecuronium may worsen respiratory function. Moreover, as shown by the TOF ratio just before the administration of the intubating dose of vecuronium being as low as 0.71 and 0.79 in two patients in our group A, it appears that respiratory function may frequently be impaired after the priming dose given prior to the insertion of the epidural catheter. After the administration of the priming dose of vecuronium, anesthetists need to observe the patient carefully for the presence of the symptoms of paralysis during the insertion of the epidural catheter.

It has been reported that calcium channel blockers enhance the action of neuromuscular relaxants [13]. If a priming dose of vecuronium is given before the insertion of the epidural catheter in patients who are receiving calcium channel blockers, undesirable symptoms of paralysis may frequently be observed. Probably, in such patients, a priming dose of vecuronium should not be given before the insertion of the epidural catheter.

In conclusion, when a priming dose of vecuronium 0.01 mg·kg^{-1} is administered 16 ± 3 min before the intubating dose of vecuronium, the time to onset of neuromuscular block is shorter than when the commonly recommended priming interval of 4 min is employed.

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