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Target controlled priming for rapid onset of intubation dose: a new approach

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Abstract

Purpose. To determine the pattern of onset of the intubating dose when given at a monitored target priming block in either phase of the priming drug effect.

Methods. Sixty consenting ASA I and II patients were premedicated by intramuscular buprenorphine ($5\,\mu g \cdot kg^{-1}$) 1 h before surgery. Neuromuscular junction monitoring was done by stimulating the ulnar nerve at the wrist using Myotest and recording the adductor pollicis response on Myograph-2000. After stabilization of the twitch tension at the titrated supramaximal stimulus (1 Hz), double-burst stimuli (DBS) were given to monitor the priming effect of vecuronium bromide (Vb) ($0.015\,mg \cdot kg^{-1}$). The DBS ratio (DBSr = D_2/D_1) was calculated for the DBS response, repeated at 20 s. Depending on the target priming block level (DBSr 0.8, 0.6, or 0.5) and the phase of the priming block to give an intubating dose of Vb ($0.8\,mg \cdot kg^{-1}$) injection, all patients were randomly assigned to six study groups: group 1 (DBSr 0.8), group 3 (DBSr 0.6), and group 5 (DBSr 0.5) during the priming block progression phase (before peak D_1 suppression), and group 2 (DBSr 0.8), group 4 (DBSr 0.6), and group 6 (DBSr 0.5) during the priming block regression phase (after peak D_1 suppression). Anesthesia was induced by thiopental ($5–7\,mg \cdot kg^{-1}$) just before the intubating dose. The effect of the intubating dose on twitch stimuli (1 Hz) was monitored.

Results. We observed that in spite of significantly variable priming intervals for identical DBSr in two different phases, the onset time of the intubating dose to 0 response was identical in similar DBSr group patients; i.e., at 0.8 DBSr, 65.0 ± 5.2 s (group 1) *vs* 66.0 ± 8.0 s (group 2); at DBSr 0.6, 55.2 ± 3.7 s (group 3) *vs* 55.2 ± 4.9 s (group 4); and at DBSr 0.5, 43.5 ± 4.8 s (group 5) *vs* 43.5 ± 4.2 s (group 6). At 0 twitch response, the intubating conditions were comparable in patients of the six groups.

Conclusion. In conclusion, target controlled priming (DBSr) for administration of the intubating dose appears to be a useful double-vision sign to predict the onset of the effect of the intubating dose precisely.

Key words: Priming, Neuromuscular monitoring, Double-burst stimulation, Vecuronium

Introduction

The priming principle refers to the injection of a subparalyzing dose of nondepolarizing neuromuscular blocking agent (NMBA) 3 to 5 min before the intubating dose [1,2]. Several studies have recommended different priming intervals in combination with varied priming and intubating doses [1–7]. The precise time interval, therefore, requires further definition. A remarkable variability in the response of patients to NMBA has been experienced. Therefore, a fixed priming time interval could be a poor predictor of acetylcholine (ACh) receptor blockade by the priming dose. It was hypothesized that the predictability of the onset time of the intubating dose could be improved by giving it at monitored priming blocks.

We have observed that during the priming dose effect, the double-burst stimulation (DBS) test (two bursts of three 50-Hz stimuli at a 750-ms interval) was more sensitive to quantify the priming dose effect than the train-of-four (TOF) test, and an identical DBS ratio (DBSr) [the second burst (D_2) divided by the first (D_1)], measuring tetanic fade, was observed in the two phases of the priming dose effect, i.e., the block progression phase (before peak D_1 suppression) and the block regression phase (after peak D_1 suppression) [8].

The present study was designed to determine the feasibility and consistency of target controlled priming to predict the rapid onset of the intubating dose of NMBA.

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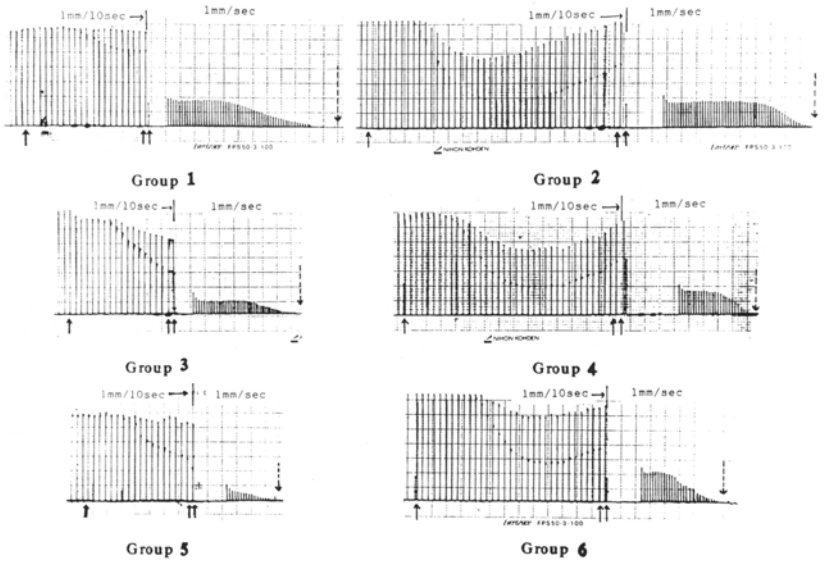

Fig. 1. Typical myograms of patients in six study groups. (↑) Priming dose (vecuronium 0.015 mg·kg^{-1}); (↑↑) intubating dose (vecuronium 0.08 mg·kg^{-1}); (↓) intubation time; priming interval between (↑) and (↑↑); intubation interval between (↑↑) and (↓). See Table 1 for demographic data on patients

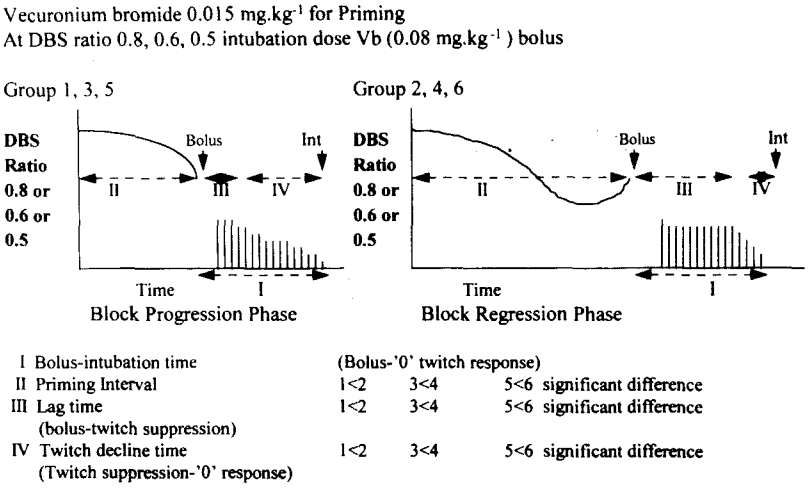

Fig. 2. Schematic representation of different events in study design and the derived parameters calculated from the myograms. DBS, double-burst stimuli

Materials and methods

Approval for the study protocol was obtained from our institute's ethical committee on clinical investigations, and prior informed consent was obtained from all patients. Patients who were receiving medications (antiepileptics or Ca^{+}-channel blockers) known to interact with NMBA or who were suffering from neuromuscular disorders were excluded from the study.

All 60 ASA I or II adult (22 to 58 years old) patients scheduled for surgery were given intramuscular buprenorphine (5 μg·kg^{-1}) 1 h before anesthesia. In the operating room, intravenous diazepam (0.1 mg·kg^{-1}) was supplemented to facilitate neuromuscular junction (NMJ) monitoring. The ulnar nerve was stimulated at the wrist by surface electrodes using Myotest-DBS. At 250 to 300 g pretension on the thumb, the adductor pollicis response was recorded using a force displacement transducer on Myograph-2000 (Biometer, Denmark). Twitch tension was stabilized at titrated supramaximal square-wave stimuli of 0.2-ms width at 1 Hz, and the DBS monitoring was started. Twitch gain was readjusted to give a D_1 of 1.00 on the myograph display. DBSr (D_2/D_1) was calculated by a Casio pocket calculator (Fx-100) with each DBS stimulus repeated at 20 s.

All medications were given intravenously into the antecubital vein of the hand opposite the site of NMJ monitoring. Three priming block targets (DBSr 0.8, 0.6, and 0.5) were randomly selected during intravenous priming by vecuronium bromide (Vb) (0.015 mg·kg^{-1}). All patients were given oxygen through a face mask,

and SpO_2 was kept over 98% by pulse oximetry. Anesthesia was induced by intravenous sodium thiopental (3–5 mg·kg^{-1}) followed by an intubating dose of Vb (0.08 mg·kg^{-1}) at DBSr targets in either priming phase. Its effect was monitored by 1-Hz stimuli (Figs. 1 and 2).

All patients were randomly allocated into six groups. The intubating dose was given at 0.8, 0.6, and 0.5 DBSr targets in the block progression phase (before peak D_1 suppression) in patients of groups 1, 3, and 5, respectively. An identical intubating dose was given at the same priming block targets in patients of groups 2, 4, and 6, respectively, but in the block regression phase (after peak D_1 suppression) (Figs. 1 and 2).

Since all the events were objectively monitored on the myograph, the control groups of either no priming or fixed-interval priming were omitted. Pulse oximetry, electrocardiograph lead II, and noninvasive arterial blood pressure were monitored throughout the study period. While blinded for the group, the first author assessed the intubating conditions on a four-point scale as described by Mirakhur and associates [9]: *excellent*, good jaw relaxation, vocal cords open, no response to intubation; *satisfactory*, good jaw relaxation, vocal cords open, minimum coughing on intubation; *fair*, jaw relaxed, cords moving, intubation requiring firm pressure and accompanied by marked coughing on intubation; *poor*, intubation impossible due to poor jaw relaxation and/or closed vocal cords.

We also observed side effects of priming and recorded the following parameters from the myograph: priming interval (from priming dose to intubating dose injection), onset of intubating dose to 0 twitch response, lag time of intubating dose effect (from intubating dose to observed twitch suppression), and twitch decline time (from observed twitch suppression to 0 response) (Fig. 2).

Values are given as mean ± SD. Statistical comparison among groups was performed by one-way analysis of variance (ANOVA). Student's t test was used to compare mean values. P values <0.05 were considered statistically significant.

Table 1. Demographic data for patients

Group	Priming block (DBSr)	Age (yr) (mean ± SD)	Male/female	Weight (kg) (mean ± SD)
1	0.8 Pr.Ph.	43 ± 14	5/5	51 ± 8
2	0.8 Rr.Ph.	45 ± 15	5/5	51 ± 10
3	0.6 Pr.Ph.	41 ± 12	5/5	51 ± 10
4	0.6 Rr.Ph.	43 ± 12	6/4	57 ± 12
5	0.5 Pr.Ph.	49 ± 11	6/4	57 ± 11
6	0.5 Rr.Ph.	47 ± 11	4/6	54 ± 11

Pr.Ph., Block progression phase; Rr.Ph., block regression phase; DBSr, double-burst stimulation ratio (D_2/D_1).

Table 2. Priming interval, onset time of intubating dose to 0 twitch response, and intubating conditions in different groups (mean ± SD)

Group	Priming block (DBSr)	Priming interval (s)	Onset time of intubating dose (s)	Intubating conditions (no. of patients)
1	0.8 Pr Ph	368 ± 122*	65.0 ± 5.2	excellent—9 good—1
2	0.8 Rr Ph	648 ± 121	66.0 ± 8.0	excellent—10 good—0
3	0.6 Pr Ph	404 ± 139*	55.2 ± 3.7	excellent—10 good—0
4	0.6 Rr Ph	628 ± 198	55.2 ± 4.9	excellent—9 good—1
5	0.5 Pr Ph	426 ± 123	43.5 ± 4.8	excellent—10 good—0
6	0.5 Rr Ph	576 ± 133	43.5 ± 4.2	excellent—8 good—2

* $P < 0.05$ compared with similar DBSr group.

Table 3. Intubating dose effect pattern in different study groups. Times in seconds (mean ± SD)

Group[a]	Total onset of intubating dose	Intubating dose effect	
		Lag time	Twitch decline time
1	65.0 ± 5.2	27.8 ± 2.5**	37.2 ± 2.6
2	66.0 ± 8.0	47.4 ± 5.6	18.6 ± 2.4**
3	55.2 ± 3.7	34.4 ± 2.3**	21.1 ± 1.4
4	55.2 ± 4.9	42.6 ± 4.0	12.6 ± 1.1**
5	43.5 ± 4.8	25.5 ± 2.0*	18.0 ± 2.7
6	43.5 ± 4.2	27.2 ± 2.3	15.6 ± 1.9*

* $P < 0.05$; ** $P < 0.001$.
[a] Groups compared: 1 and 2, 3 and 4, 5 and 6.

Results

Patients in all six study groups were similar in age, weight and sex (Table 1). Representative myograms recorded from patients of the six groups are depicated in Fig. 1. The study design is also schematically represented in Fig. 2.

The onset time of the intubating dose to 0 twitch response was similar in patients of identical DBSr groups, i.e., in group 1 *vs* 2, group 3 *vs* 4, and group 5 *vs* 6, in spite of significantly different priming intervals (Table 2). The onset time of the intubating dose was fastest (43.5 ± 4.8s) and significantly shorter at 0.5 DBSr than at 0.6 to 0.8 DBSr (Table 2). The intubating conditions were comparable in patients of each group, and overall intubation was excellent in 56 (93.3%) patients and good in the rest of the patients (Table 2).

The lag time of the intubating dose effect was significantly longer ($P < 0.01$) with quicker twitch decline time in patients in whom the intubating dose was injected in the priming block regression phase (groups 2, 4, and 6) than in the patients of the respective DBSr groups of the block progression phase (groups 1, 3, and 5), while the total time of onset of the intubation dose was similar (Table 3).

The side effects of priming were comparable in patients of all six groups, and overall 48 (72.7%) patients complained of visual disturbances or difficulty in opening the eyes or protruding the tongue.

Discussion

A high margin of safety for the failure of neuromuscular transmission is observed in skeletal muscles [10,11]. Priming is aimed at reducing the functional ACh receptors at the NMJ by giving a subclinical dose of NMBA. Up to now emphasis has been placed on getting an appropriate combination of priming dose, priming interval, and intubating dose to achieve intubation within 1 min. Unfortunately, no consensus has been formed [1–7]. The variable response to NMBA in patients might be the reason for this. We too have observed wide SD values for the onset time for target priming block (DBSr) targets >100s (Table 2), thus highlighting the limitation of the priming time interval concept that has been explored up to now.

It is noteworthy that the onset time of the intubating dose was similar when it was given at the same target DBSr, in spite of significantly variable priming intervals. Since the dose-response curve of NMBA is sigmoid-shaped and rapid NMJ transmission failure occurs after 75% ACh receptor block [12], any method of monitoring the extent of ACh-receptor block should be able to predict the extent of the block accurately. Tetanic fading has been reported to closely monitor the extent of ACh-receptor block [13,14]. DBS is a tetanic test [15], and DBSr precisely measures tetanic fade, so the monitored DBSr target gave a better estimate of the extent of ACh-receptor block at the NMJ and thus the constant onset time of the intubating dose at fixed DBSr. In addition, the faster onset of the intubating dose in patients with lower DBSr (0.5), indicating more tetanic fade or more ACh-receptor blockade, further supported this correlation.

In spite of the similar onset times, the different onset patterns of the intubating dose effect in patients with block progression versus block regression is interesting. The lag time for the intubating dose effect was shorter with prolonged twitch decline during block progression than regression. In the priming block regression phase or prolonged priming interval, the intubating dose is likely to take longer to increase drug levels to initiate response suppression, where already efflux from the receptor site would have started due to drug redistribution. On the contrary, during the block progression phase, the intubating dose would quickly increase Vb levels to initiate twitch suppression over the Vb plasma levels attained by the priming dose. As the difference between priming intervals of patients in groups 5 and 6

was less, the lag time of the intubating dose effect was also less different. This further supported the above explanation for the observed phenomenon.

However, since tetanic fade has been correlated with the extent of Ach-receptor blockade or loss of margin of safety [10,11], at identical fade or DBSr, the onset of the repeat dose remained similar.

In conclusion, the priming block measured by DBSr could be a better alternative double-vision sign to predict accurately the onset time of the intubating dose.

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