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Interaction of sevoflurane, isoflurane, enflurane and halothane with non-depolarizing muscle relaxants and their prejunctional effects at the neuromuscular junction.

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Abstract

The interaction of four inhalational anesthetics (sevoflurane, isoflurane, enflurane and halothane) with pancuronium and vecuronium and also their prejunctional actions at the neuromuscular junction were quantitatively studied using rat phrenic nerve-hemidiaphragm preparations. To investigate the prejunctional effects of inhalational anesthetics, a train-of-four ratio (T4/T1) and the tetanus ratio (the ratio of the final response to the initial response during tetanus) were evaluated. All four inhalational anesthetics markedly potentiated the neuromuscular blockade of twitch response caused by either pancuronium or vecuronium with halothane and enflurane being the most potent both on a % concentration basis and on a MAC (minimum alveolar concentration) basis. Although none of the four inhalational anesthetics had any effects on the T4/T1 ratio, they produced variable effects on the tetanus ratio. Sevoflurane had little effect on the tetanus ratio, whereas 1 and 2% isoflurane and 1, 2 and 3% enflurane increased the tetanus ratio and 5% halothane and 5% enflurane significantly reduced the tetanus ratio. Halothane and enflurane had the most potent depressant action of the four inhalational anesthetics both on the % concentration basis and on the MAC basis. These results indicate that the main site of action of inhalational anesthetics is a postjunctional site at the neuromuscular junction and that they do not seem to act on prejunctional sites at the concentrations used in clinical situations.

KEYWORDS: inhalational anesthetics, muscle relaxants, drug interaction, neuromuscular transmission

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Interaction of Sevoflurane, Isoflurane, Enflurane and Halothane with Non-Depolarizing Muscle Relaxants and their Prejunctional Effects at the Neuromuscular Junction

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The interaction of four inhalational anesthetics (sevoflurane, isoflurane, enflurane and halothane) with pancuronium and vecuronium and also their prejunctional actions at the neuromuscular junction were quantitatively studied using rat phrenic nerve-hemidiaphragm preparations. To investigate the prejunctional effects of inhalational anesthetics, a train-of-four ratio (T4/T1) and the tetanus ratio (the ratio of the final response to the initial response during tetanus) were evaluated. All four inhalational anesthetics markedly potentiated the neuromuscular blockade of twitch response causd by either pancuronium or vecuronium with halothane and enflurane being the most potent both on a % concentration basis and on a MAC (minimum alveolar concentration) basis. Although none of the four inhalational anesthetics had any effects on the T4/T1 ratio, they produced variable effects on the tetanus ratio. Sevoflurane had little effect on the tetanus ratio, whereas 1 and 2% isoflurane and 1, 2 and 3% enflurane increased the tetanus ratio and 5% halothane and 5% enflurane significantly reduced the tetanus ratio. Halothane and enflurane had the most potent depressant action of the four inhalational anesthetics both on the % concentration basis and on the MAC basis. These results indicate that the main site of action of inhalational anesthetics is a postjunctional site at the neuromuscular junction and that they do not seem to act on prejunctional sites at the concentrations used in clinical situations.

Key words : **inhalational anesthetics, muscle relaxants, drug interaction, neuromuscular transmission**

Various inhalational anesthetics have a potent depressant action on neuromuscular transmission (1-12). Recently, a new inhalational anesthetic, sevoflurane has been introduced into Japan, and extensive clinical and laboratory studies are under way (9-12). However, there have been no quantitative comparisons of sevoflurane with halothane, enflurane and isoflurane with regard to their interaction with muscle relaxants. In addition, no author has reported on the prejunctional effects of sevoflurane at the neuromuscular junction. In this experiment using rat phrenic nerve-hemidiaphragm preparation, we quantitatively compared sevoflurane with halothane, enflurane and isoflurane with regard to their relative effects on the neuromuscular blockade induced by either

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pancuronium or vecuronium. We also evaluated their prejunctional effects at the neuromuscular junction in terms of a train-of-four ratio (T4/T1) and the tetanus ratio in the presence of inhalational anesthetics at various concentrations.

Materials and Methods

The experiments were performed on phrenic nerve-hemidiaphragm preparations excised from decapitated male Sprague-Dawley rats of 250–350 g body weight. The preparations were suspended in double walled glass organ baths filled with modified Krebs' solution (13) (NaCl 113.0; KCl 4.7; $CaCl_2$ 1.4; KH_2PO_4 1.2; $MgSO_4$ 1.2; $NaHCO_3$ 25.0; glucose 1.5 mM). The solution was kept at 37°C and aerated with 95% oxygen and 5% carbon dioxide. Phrenic nerves were stimulated with supramaximal square wave pulses of 0.2 msec duration at 0.1 Hz. The indirectly elicited isometric twitch tension was continuously monitored with B-611T force displacement transducers and recorded on an RM-6000 polygraph (Nihon Kohden Co., Tokyo, Japan). After the twitch tension stabilized, the experiments were performed.

First, control studies were performed to determine the doses of pancuronium (Organon Co., Tokyo, Japan) and vecuronium (Organon Co.) effective in producing a 50% depression of twitch height (ED_{50}) in the absence of inhalational anesthetics. A single dose-response method was employed, in which one dose of a muscle relaxant was administered once to a preparation in the bath. Accordingly, one dose-response value was obtained from each preparation. We chose doses of pancuronium and vecuronium that would provide a three-point dose-response curve, from which the ED_{50} was obtained by the least- square method. Similarly, ED_{50}s of both relaxants were determined one hour after administration of each inhalational anesthetic via a Copper Kettle vaporizer connected to a bubbling tube which entered the bath.

Measurements were taken at the three different concentrations, 1%, 2% and 3% of each inhalational anesthetic. The concentration of the anesthetic gas was continuously monitored with an Engstrom gas analyzer (Tokibo Co., Ltd., Tokyo, Japan), which was calibrated by gas chromatography and maintained at the preset value throughout the experiment. In addition, the concentration of inhalational anesthetics in the bath was measured by gas chromatography (Shimadzu GC 6AMPrTF) to ensure that the concentration of inhalational anesthetics in the bath equaled that in the kettle (Table 1) (14).

Table 1 The concentrations of inhalational anesthetics in the bath determined by gas chromatography

Drugs (%)		Concentration in the bath (μg/ml)
Sevoflurane		
	1	4.34 ± 0.08
	2	9.42 ± 0.55
	3	12.1 ± 0.70
Isoflurane		
	1	2.91 ± 0.07
	2	5.38 ± 0.15
	3	7.15 ± 0.22
Enflurane		
	1	3.46 ± 0.20
	2	5.91 ± 0.70
	3	9.45 ± 1.85
Halothane		
	1	4.44 ± 0.12
	2	8.84 ± 0.22
	3	11.3 ± 0.67

Values are the mean ± SE(n=4)

Another experiment using the same set-up was performed in order to assess the prejunctional effect of the inhalational anesthetics, after each anesthetic had been administered for one hour. A train-of-four stimulation (supra-maximal square wave pulses of 0.2 msec duration at 2 Hz) for 2 sec followed by a tetanic stimulation (supra-maximal square wave pulses of 0.2 msec duration at 50 Hz) for 2 sec was applied to the preparations in order to determine the T4/T1 ratio and the tetanic fade ratio defined as the ratio of the final response to the initial response during the tetanus. This experiment was performed at four different concentrations (1%, 2%, 3%, 5%) of each inhalational anesthetic. Control values of the T4/T1 and tetanus ratios were determined in the absence of inhalational anesthetics. A typical trace in the presence of halothane is shown in Fig. 1.

Comparisons of the control group and the groups which received inhalational anesthetics were made by a one-way analysis of variance with Bonferoni modification (15). A value of $p < 0.05$ was considered to be significant.

Results

As shown in Table 2 and Fig. 2, all four

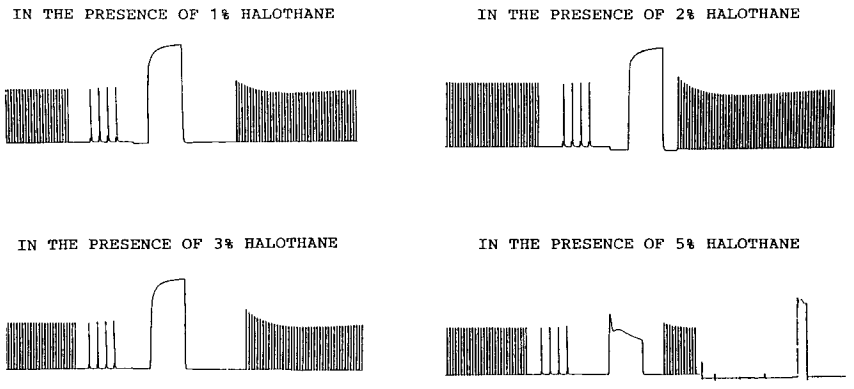

Fig. 1 A typical trace in the presence of 1, 2, 3 and 5 % halothane.
After a stable twitch height was obtained, a train-of-four stimulation (2 Hz) for 2 sec followed by a tetanus stimulation (50 Hz) for 2 sec was applied. Sensitivity was reduced by 50 % for the tetanus stimulation. The tracing rate was 5 mm/min at 0.1 Hz stimulation and 30 mm/min at either 2 Hz or 50 Hz stimulation.

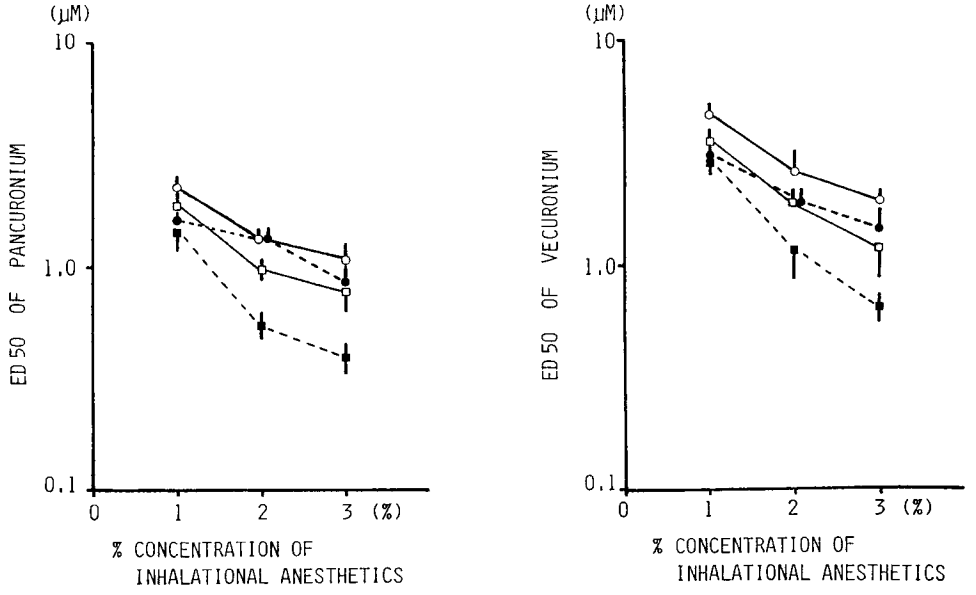

Fig. 2 The effects of various concentrations of inhalational anesthetics on ED_{50} values for pancuronium and vecuronium. (○—○), Sevoflurane; (●---●), Isoflurane, (□—□), Euflurane; (■---■), Halothane. All values are the mean (95 % confidence limits)

inhalational anesthetics decreased the ED_{50}s of vecuronium and pancuronium in a dose-dependent manner compared with those of the control. The order of potency estimated on the basis of % concentration was halothane > enflurane = isoflurane > sevoflurane, and that on the basis of MAC (1 MAC) was enflurane > sevoflurane = halothane = isoflurane (Fig. 3). The choice of the muscle relaxant did not significantly affect the potency order.

As shown in Table 3, none of the inhalational anesthetics altered the T4/T1 ratio significantly at any concentration. On the other hand, the tetanus ratio varied depending on the type of inhalational anesthetic administered (Fig. 4). Although 5 % enflurane and 5 % halothane decreased the tetanus ratio significantly ($p < 0.01$), 1, 2 and 3 % enflurane, 1 and 2 % isoflurane and 3 %

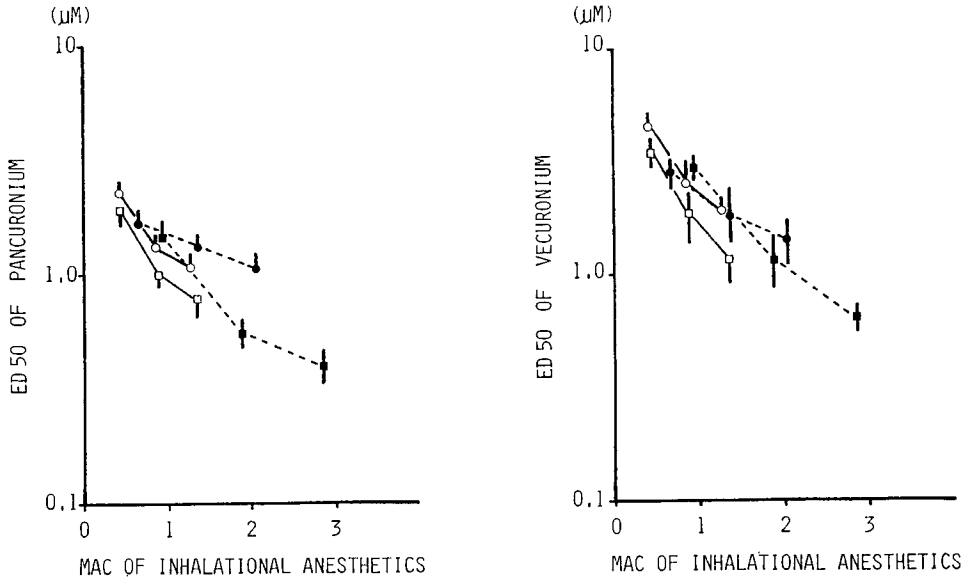

Fig. 3 The effects of various MACs of inhalational anesthetics on ED_{50} values of pancuronium and vecuronium. (○—○), Sevolflurane; (●---●), Isoflurane; (□—□), Euflurane; (■---■), Halothane. Values are the mean (95 % confidence limits).

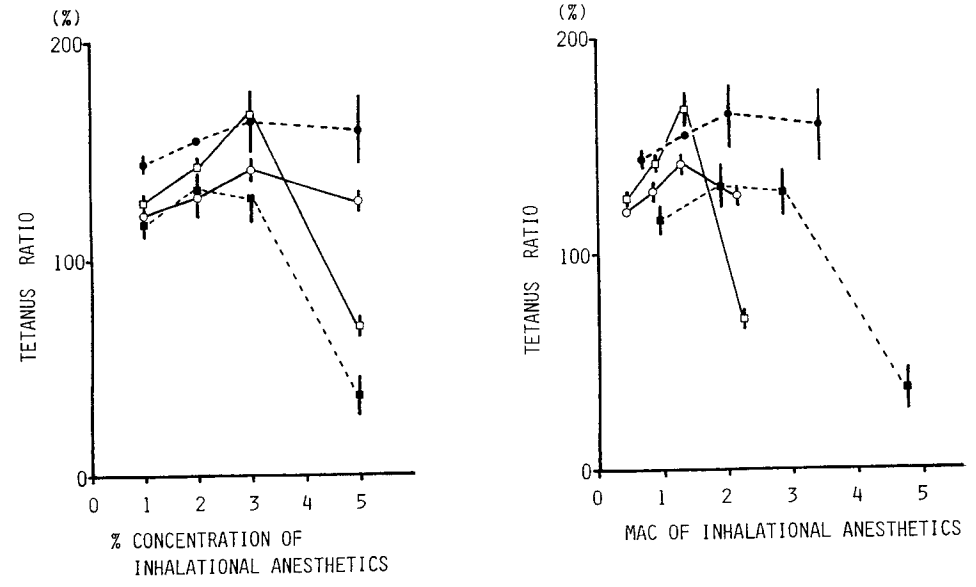

Fig. 4 The effects of inhalational anesthetics on the tetanus ratio. (○—○), Sevoflurane; (●---●), Isoflurane; (□—□), Euflurane; (■---■), Halothane. Values are the mean ± SE of four experiments.

sevoflurane increased the tetanus ratio. Enflurane was more potent than halothane in reducing the tetanus ratio when estimated on the MAC basis. Sevoflurane and isoflurane did not reduce the tetanus ratio at any concentration tested.

Table 2 Effects of inhalational anesthetics on ED_{50} values of pancuronium and vecuronium

Drugs (%)		ED_{50} of Pancuronium (μM)	ED_{50} of Vecuronium (μM)
Control		3.24 (2.99−3.49)	5.33 (4.68−5.97)
Sevoflurane	1	2.29 (1.98−2.59)	4.63 (4.14−5.12)
	2	1.33 (1.18−1.48)	2.56 (1.92−3.20)
	3	1.07 (0.90−1.24)	1.94 (1.79−2.09)
Isoflurane	1	1.67 (1.51−1.85)	2.86 (2.46−3.21)
	2	1.34 (1.23−1.47)	1.87 (1.43−2.47)
	3	0.86 (0.72−1.05)	1.43 (1.14−1.79)
Enflurane	1	1.91 (1.64−2.19)	3.49 (3.04−3.94)
	2	0.99 (0.92−1.06)	1.88 (1.38−2.37)
	3	0.77 (0.63−0.90)	1.17 (0.92−1.43)
Halothane	1	1.44 (1.16−1.71)	3.01 (2.65−3.37)
	2	0.55 (0.48−0.63)	1.16 (0.85−1.46)
	3	0.39 (0.33−0.45)	0.65 (0.56−0.74)

Values are the mean (95 % confidence limits). Sample sizes varied from 6 to 8.

Table 3 Effects of inhalational anesthetics on the T4/T1 ratio and tetanus ratio

Drugs (%)		T4/T1 ratio(%)	Tetanus ratio (%)
Control		100.0 ± 0.0	113.8 ± 2.6
		104.3 ± 5.3	118.5 ± 3.0
		100.0 ± 0.0	125.8 ± 0.8
		100.0 ± 0.0	125.5 ± 4.3
Sevoflurane	1	100.0 ± 0.0	119.8 ± 0.9
	2	100.0 ± 0.0	128.8 ± 3.6
	3	101.3 ± 1.2	141.8 ± 3.2**
	5	102.3 ± 2.3	126.7 ± 4.2
Isoflurane	1	102.5 ± 0.9	144.0 ± 3.0**
	2	103.0 ± 1.3	155.0 ± 1.6**
	3	103.5 ± 2.2	164.3 ± 14.1
	5	100.0 ± 0.0	159.5 ± 16.4
Enflurane	1	102.3 ± 1.3	125.8 ± 2.7**
	2	100.0 ± 0.0	142.8 ± 3.0**
	3	100.0 ± 0.0	167.5 ± 7.6*
	5	93.2 ± 2.4	69.2 ± 4.6**
Halothane	1	103.3 ± 1.3	116.3 ± 6.3
	2	102.3 ± 1.3	131.3 ± 11.0
	3	100.0 ± 0.0	128.5 ± 11.2
	5	96.7 ± 2.2	36.8 ± 9.6**

Values are the mean ± SE(n=4) * $P<0.05$ and ** $P<0.01$ compared with the control.

Discussion

Sevoflurane is a unique inhalational anesthetic having the lowest level of blood solubility and blood gas distribution coefficient of all inhalational anesthetics, and thus, it resembles gaseous agents like N_2O and cyclopropane (9, 16, 19).

As for the interaction of inhalational anesthetics with muscle relaxants, Tai *et al.* (10), Kurita *et al.* (11) and Itagaki *et al.* (12) have reported that sevoflurane more effectively potentiated the neuromuscular blocking effect of vecuronium and pancuronium than either halothane or enflurane in man and cat. Miller and co-workers (1-4) found that enflurane was the most potent volatile anesthetic, followed by isoflurane and halothane, in augmenting vecuronium-induced neuromuscular blockade in man. Likewise, Waud reported that enflurane was the most potent, and isoflurane and halothane were equally potent in decreasing the ED_{50} of d-tubocurarine in isolated guinea pig nerve-lumbrical muscle preparations (5, 7). In our study, halothane was the most potent, followed by enflurane, isoflurane and sevoflurane. However, if these anesthetics were compared in terms of the MAC of Sprague-Dawley rats (halothane 1.05: enflurane 2.21: isoflurane 1.46: sevoflurane 2.33), calculated from the reports of Drummond (18) and Scheller *et al.* (19), we estimated that at 1 MAC, enflurane had the lowest ED_{50}s for pancuronium and vecuronium, and that sevoflurane, isoflurane and halothane had almost the same ED_{50}s. This disagreement on the potency ranking of sevoflurane and isoflurane with the other authors might be due in part to the species difference as well as the differences in the experimental settings in which a pharmacokinetic factor such as the augmentation of blood flow to the muscle is not involved (20). Although there has been no report about the effect of sevoflurane on muscular blood flow, sevoflurane might have the same effect as isoflurane.

The clinical importance of the prejunctional effects of potent inhalational anesthetics at the

neuromuscular junction has not yet been determined. However, many authors reported that inhalational anesthetics caused tetanic fade and suppressed repetitive activity generated at the motor nerve endings (21-23). Furthermore, Bowman *et al.* (24, 25) and Gibb *et al.*(26) suggested that the tetanic fade phenomena in the presence of a muscle relaxant could be the result of a diminishing output of acetylcholine from the motor nerve endings. According to Bowman's theory, during partial neuromuscular block by muscle relaxants, the "fade" phenomenon can be seen. The traditional explanation of this fade is that acetylcholine output decreases with repetitive stimulation even in the absence of muscle relaxants (physiological phenomenon), but this fade can be observed only when the margin of safety is reduced (*e.g.*, in the presence of muscle relaxants). However, from various electrophysiological and pharmacological evidence, Bowman says that there is no fade in the physiological condition and that the fade is the result of the prejunctional action of muscle relaxants. Therefore, the "fade" phenomenon indicates the prejunctional action of a given drug or a reduced margin of safety. Based on his theory, we studied the effect of inhalational anesthetics on the T4/T1 ratio as an index of neuromuscular blockade and the tetanus ratio as an index of tetanic maintenance. Though the T4/T1 ratio was not affected by any of the inhalational anesthetics, the tetanus ratio was influenced in a different way by each inhalational anesthetic. Five percent enflurane and 5% halothane both decreased the tetanus ratio significantly. On the other hand, 1 to 3% enflurane and 1 to 2% isoflurane augmented the ratio, and sevoflurane had the same tendency. There are two possible explanations for this phenomenon. First, the inhalational anesthetics might have a biphasic action on the nerve endings, increasing at low concentrations and decreasing at high concentrations the output of acetylcholine from nerve endings. However, there has been no report on this action, and further investigation is needed. Second, the increase in the tetanus ratio might be entirely due to the action of inhalational anesthetics on muscle itself, and have no relation to the prejunctional action. Waud (6), Beeler *et al.* (27) and Nelson *et al.* (28) found that inhalational anesthesics were able to facilitate the excitation-contraction coupling in the muscle through the Ca^{2+} channel at the sacroplasmic reticulum membrane of the muscle at a low concentration and, on the contrary, depress it at a high concentration. If this is the case, the decrease in the tetanus ratio might be due to the action of inhalational anesthetics on muscle. However, according to Waud (6) and Ohta (personal communication), a concentration of more than 5% was needed to depress a directly-stimulated muscle contracture. Therefore, the decrease in the tetanus ratio in the presence of a high concentration of halothane and enflurane is considered to be mainly the prejuntional action of inhalational anesthetics.

According to our results, it is likely that halothane and enflurane have potent depressant actions on nerve endings when estimated either on the % concentration basis or the MAC basis. Isoflurane has some facilitating action on the contractile mechanism but does not have any significant effect on the nerve endings. Considering the concentrations at which inhalational anesthetics exert their prejunctional action and the absence of depression of the T4/T1 ratio, it is unlikely that their prejunctional action is relevant to their clinical use. Furthermore, considering the low concentration of inhalational anesthetics in potentiating the neuromuscular blockade induced by muscle relaxants, together with the elctrophysiological measurement (5, 29, 30), it is suggested that the main site of action of inhalational anesthetics is the postjunctional site at the neuromuscular junction. However, from this experiment, we can not completely rule out the possibility that the prejunctional effect of the inhalational anesthetics, enflurane in particular, might be involved in the inhibition of neuromuscular transmission in the clinical situation. Therefore, in general anesthesia using both inhalational anes-

thetics and muscle relaxants, we must be vigilant with regard to any residual block, knowing that the inhalational anesthetics act on various sites at the neuromuscular junction (6, 31)

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