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The Infusion Rate of Mivacurium or Atracurium for Cesarean Section Compared with Gynecological Procedures

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Abstract

Mivacurium is mainly metabolized by plasma cholinesterase, whereas atracurium is removed by Hofmann elimination. The purpose of this study was to compare the infusion rate of atracurium and mivacurium in maintaining surgical relaxation, and to compare their recovery indices between parturients and non-pregnant women. Muscle relaxation was maintained by the continuous infusion of relaxants to retain the first response of train-of-four (TOF) at 5% of control. When mivacurium was used, Bolus-T_5 (duration from the end of mivacurium bolus injection to 5% single twitch recovery) was measured. After discontinuing the infusion, the recovery index was measured. The infusion rate of mivacurium, not atracurium, was significantly lower in parturients and Bolus-T_5 of parturients was significantly longer than that of non-pregnant women. There was no significant difference in the recovery indices of both relaxants. The authors concluded that the infusion rate of mivacurium in maintaining muscle relaxation in parturients should be reduced compared to the rate in non-pregnant women and measuring Bolus-T_5 may be helpful in determining the infusion rate to maintain muscle relaxation.

Key Words: Neuromuscular block, mivacurium, atracurium, cesarean section, plasma cholinesterase

INTRODUCTION

Mivacurium is a new nondepolarizing muscle relaxant with a bisquaternary benzylisoquinolium structure resembling that of atracurium and doxacurium.[1] It is almost completely hydrolyzed by plasma cholinesterase (pChe) and the hydrolysis rate of mivacurium is 70% that of succinylcholine.[2] Atracurium is also a nondepolarizing muscle relaxant and is metabolized by Hofmann elimination.[3] The reaction is a purely chemical one accelerated by alkaline pH and an increase in temperature. Some degree of enzymatic ester hydrolysis (not related to pChe) also probably occurs.[4,5]

There are many physiologic changes in the mother during pregnancy, including an increase in whole blood and plasma volume, a decrease in hepatic blood flow,[6] an increase in the glomerular filtration rate and renal blood flow,[7] and a decrease in pChe activity.[8] Therefore, the dose of relaxants to maintain surgical relaxation in pregnant women may be different from that of non-pregnant women, but the extent of the difference varies according to the relaxants. We therefore designed a study to compare the difference in the infusion rate of atracurium and mivacurium in maintaining surgical relaxation, and to compare their recovery indices from relaxation between parturients and non-pregnant women.

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MATERIALS AND METHODS

We studied 40 ASA physical status I female patients undergoing elective surgery. Twenty of them were full-term pregnant women undergoing cesarean section. The remaining patients were undergoing elective gynecological procedures. Muscle relaxation was maintained by mivacurium for 10 patients in each group and by atracurium in the others. All patients were free of neuromuscular diseases and were not receiving any medication known to alter neuromuscular transmission.

Glycopyrrolate 0.2 mg was administered intramuscularly for premedication about 30 minutes before induction of anesthesia. Anesthesia was induced with 2.5% thiopental sodium 4 mg/kg, followed by suc-

cinylcholine 1.5 mg/kg to facilitate endotracheal intubation. Anesthesia was maintained with enflurane (0.8−1% end-tidal concentration), oxygen (50%) and nitrous oxide (50%). Midazolam 5 mg and fentanyl 100 μg were injected after umbilical cord ligation in parturients and after same time interval in non-pregnant women.

We used an accelerograph (TOF GUARD®, Organon, Veedijk, Belgium) to evaluate muscle relaxation. Stimulating electrodes were placed over the ulnar nerve at the left wrist and a ceramic response sensor was attached at the left thumb. After obtaining supramaximal stimuli and control twitch height by gradually increasing electric current, train-of-four (TOF) stimulation was delivered at 15-second intervals until the end of each study. Skin temperature over the thenar muscle was monitored continuously and maintained at between 35°C and 36°C.

Mivacurium 0.15 mg/kg was injected just after full recovery from muscle relaxation by succinylcholine.

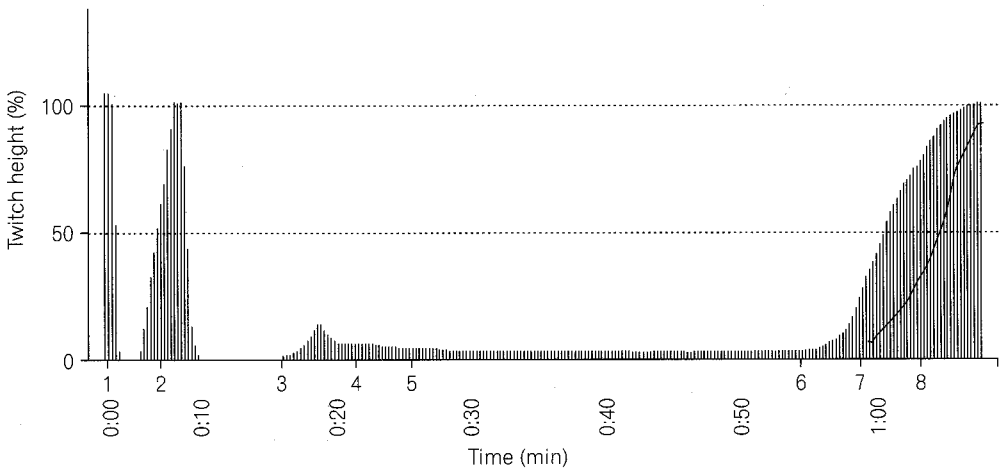

Fig. 1. Measurement of muscle contraction during mivacurium infusion and recovery by accelerograph. 1: Succinylcholine bolus administration. 2: Mivacurium bolus administration (0.15 mg/kg). 3: Infusion start. 4: First adjustment of infusion rate. 5: Second adjustment of infusion rate (T1=5% of control). 6: Infusion stop. 7: T1=25% of control. 8: T1=75% of control. TOF ratio is marked by dotted line.

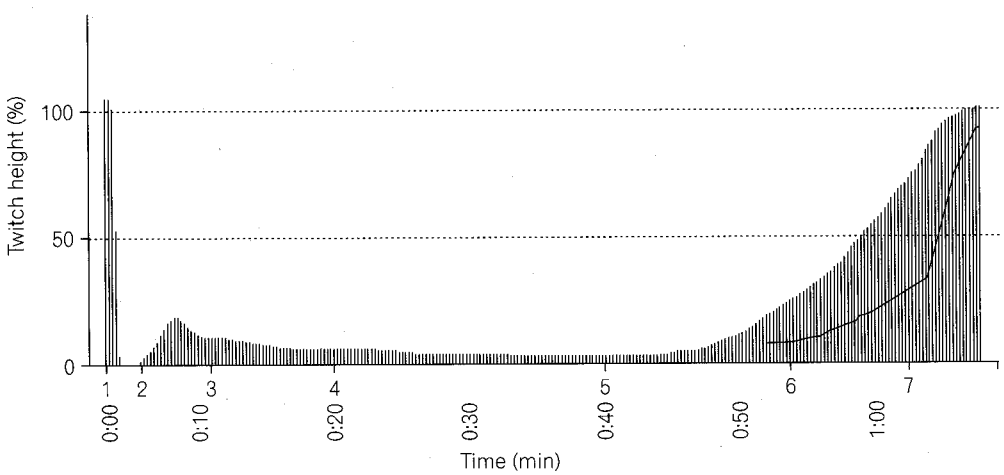

Fig. 2. Measurement of muscle contraction during atracurium infusion and recovery by accelerograph. After measuring the recovery index, pyridostigmine 0.2 mg/kg and glycopyrrolate 0.008 mg/kg were administered intravenously. 1: Succinylcholine bolus administration. 2: Atracurium bolus administration (0.15 mg/kg). 3: Infusion start. 4: Adjustment of infusion rate (T1=5% of control). 5: Infusion stop. 6: T1=25% of control. 7: T1=75% of control. TOF ratio is marked by dotted line.

We started mivacurium infusion after the level of the first twitch response (T1) of TOF reached 5% of control and we then adjusted the infusion rate to maintain T1 5% of control (Fig. 1). Atracurium 0.15 mg/kg was injected just after the beginning of recovery from muscle relaxation by succinylcholine. Atracurium infusion was started after the response of TOF stimulation was stabilized and the infusion rate was adjusted to maintain T1 5% of control (Fig. 2). Body weight used to calculate the infusion rate was corrected by subtracting the weight of baby, placenta and hemorrhage from the body weight measured just before surgery in cesarean section. The infusion was stopped at the end of the operation and the recovery index (recovery interval of T1 from 25% to 75% of control) was measured. When mivacurium was used, Bolus-T_5 (duration from the end of mivacurium bolus injection to recovery of T1 up to 5% of control) was measured. If atracurium was used, pyridostigmine 0.2 mg/kg and glycopyrrolate 0.008 mg/kg were administered after measuring the recovery index. The measurements were performed by anesthesiologists blinded to the relaxants used.

The data were presented as mean±SEM. Characteristics of patients, infusion rate, bolus-T_5 and recovery index were analyzed using unpaired Students *t*-tests. Linear regression was used to analyze the correlation between the infusion rate and the recovery indices of both relaxants, and between bolus-T_5 and the infusion rate of mivacurium. The correlation coefficient was also calculated. A probability value of <0.05 was considered significant.

Table 1. The Characteristics of Patients

		Parturients (n=10)	Non-pregnant women (n=10)
Atracurium	Age (yrs)	30.9±1.0	31.4±1.6
	Body wt. (kg)*	60.6±0.4†	55.5±0.5
	Height (cm)	160.8±1.7	161.7±2.0
Mivacurium	Age (yrs)	32.2±0.9	32.4±1.3
	Body wt. (kg)*	61.1±1.6†	55.6±2.2
	Height (cm)	161.2±1.4	160.9±2.1

Results are mean±SEM.
* Body weight of parturients was corrected by subtracting the weight of the baby, placenta and hemorrhage from the body weight measured just before surgery in cesarean section.
† $p<0.05$ vs. non-pregnant women.

Table 2. Infusion Rate (IR), Recovery Index (RI)* and Bolus-T_5†

		Parturients (n=10)	Non-pregnant women (n=10)
Atracurium	IR (μg/kg/min)	7.0±0.3	6.2±0.3
	RI (min)	10.3±0.8	10.9±0.8
Mivacurium	IR (μg/kg/min)	3.9±0.3‡	5.8±0.5
	RI (min)	5.5±0.2	5.6±0.2
	Bolus-T_5 (min)	10.4±0.4‡	8.6±0.4

Results are mean±SEM.
* recovery interval of first twitch response of train-of-four from 25% to 75% of control.
† duration from the end of mivacurium bolus injection to recovery of first twitch response of train-of-four recovery up to 5% of control.
‡ $p<0.05$ vs. non-pregnant women.

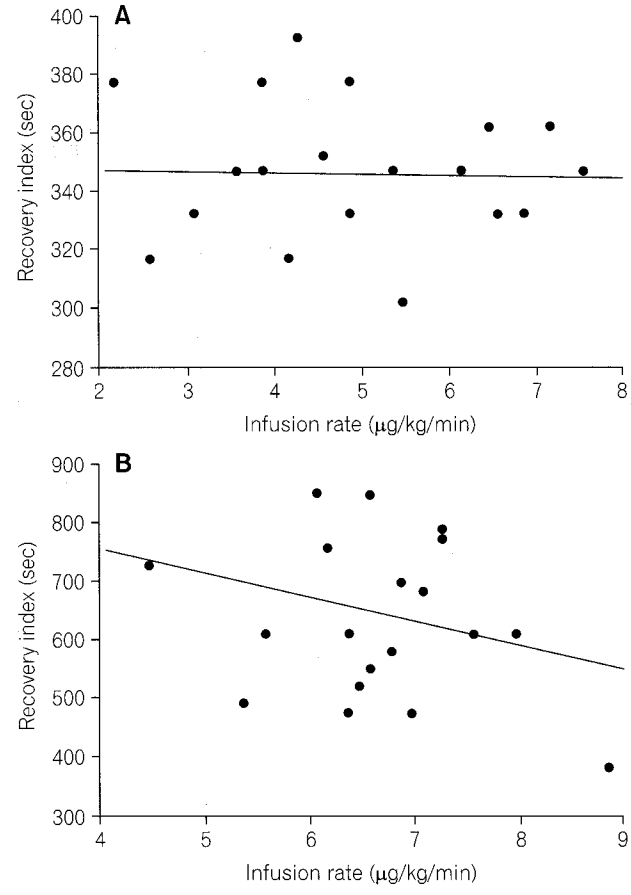

Fig. 3. Relationship between the infusion rate of muscle relaxants and recovery indices. (A) mivacurium ($r=-0.03$) and (B) atracurium ($r=-0.27$). There was no correlation between the factors.

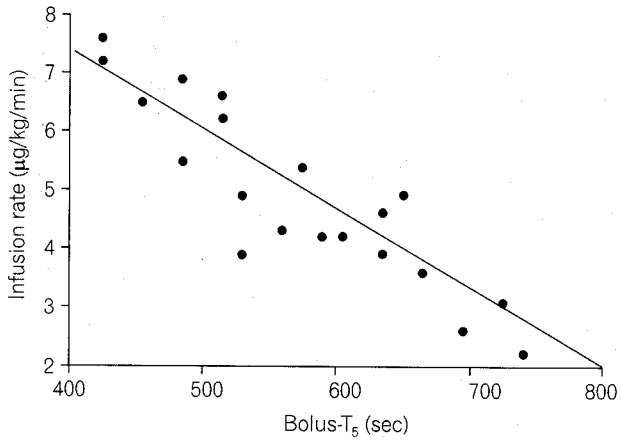

Fig. 4. Relationship between bolus-T_5 and infusion rate of mivacurium ($r = -0.90$). There was a strong negative correlation between the factors. Bolus-T_5 refers to duration from the end of mivacurium bolus injection to recovery of first twitch response of train-of-four recovery up to 5% of control.

RESULTS

The characteristics of the patients enrolled in the study are summarized in Table 1. There was no significant difference between the groups with respect to age and height, but the body weight of parturients was higher than non-pregnant women.

There was no significant difference in recovery indices and recovery times between the two groups. The infusion rate of atracurium was not significantly different between the groups, but the infusion rate of mivacurium in parturients was significantly lower than in non-pregnant women and Bolus-T_5 in parturients was significantly longer than in non-pregnant women (Table 2). There was little correlation between the infusion rate and the recovery index (Fig. 3), but there was a strong negative correlation between Bolus-T_5 and the infusion rate of mivacurium (Fig. 4).

DISCUSSION

Pregnancy is associated with major physiologic changes.[9] These changes can affect the action of muscle relaxants. Especially during cesarean section, the relatively greater degree of hemorrhage and the subsequent volume replacement, as well as removal of the infant and placenta during delivery, may substantially affect the pharmacokinetics of many drugs.[10] However, the extent of the effects may differ according to the relaxants. The distribution half-life and the volume of distribution of pancuronium were similar in normal subjects and women undergoing cesarean section, but the elimination half-life was shortened in parturients mainly due to the greater degree of hemorrhage.[11] Pregnancy-induced changes in liver blood flow and/or competition for the liver uptake of sexual hormones may interfere with the hepatic clearance of vecuronium in postpartum patients and thereby cause the prolongation of neuromuscular blockade.[12] In this experiment, the infusion rate of mivacurium in maintaining muscle relaxation was significantly low in parturients. This indicated that the actions of mivacurium were significantly affected by cesarean section.

Mivacurium is unique among non-depolarizing muscle relaxants in that it is metabolized by pChe. Many investigators have reported that pChe activity decreases during pregnancy, especially at term.[13-15] In in vitro experiment, the rate of hydrolysis of mivacurium decreased as plasma was serially diluted.[16] It has been reported that patients with impaired liver function had a significantly longer mean residence time and smaller plasma clearance than did patients with renal failure or control patients.[17] There was a significant negative correlation between pChe activity and recovery time after a single bolus injection.[18] Meanwhile the infusion rate of mivacurium was also influenced by pChe activity.[19] There have been no reports about prolonged muscle relaxation by mivacurium during cesarean section, but one case has been reported about prolonged muscle relaxation in a parturient with succinylcholine, which was also metabolized by pChe.[20] The genotype of the parturient was normal in that case, but pChe activity was just below normal. Recently Gin et al. reported that the duration of neuromuscular block by mivacurium bolus dose until 25% recovery of first twitch response was longer in the postpartum group compared with the control group, and that pChe activity decreased in the postpartum group compared with the control group.[21]

In this study we did not measure pChe activity, but according to the reports mentioned above, the infusion rate of mivacurium was probably reduced due to decreased pChe activity in parturients. We believe that increased blood volume or relatively profuse bleeding and removal of the placenta and fetus during delivery do not have a significant influence on the infusion rate of mivacurium because

the infusion was started after delivery. Body weight estimation of patients may affect the infusion rate of relaxants because, in parturients, the portion of lean body mass in body weight is less than in non-pregnant women. Small differences in the atracurium infusion rate (not statistically significant) may be explained by this, but the difference in the mivacurium infusion rate was much greater than the difference in the atracurium infusion rate. Induction of the hepatic microsomal mixed function oxidase system or a decrease in hepatic blood flow during pregnancy also did not significantly affect the metabolism of mivacurium because it is not metabolized in the liver. Other physiologic changes during pregnancy or cesarean section may also have some effects on the metabolism of mivacurium, but we think that decreased pChe activity in parturients is the dominant effect.

Interestingly, Bolus-T_5 was prolonged in parturients, but the recovery index of parturients was similar to non-pregnant women. It meant that the duration of muscle relaxation by bolus dose of mivacurium was prolonged during cesarean section, but that once recovery began, the recovery rate was no different from gynecological surgery. The infusion rate of relaxants also did not affect the recovery index. It meant that recovery from relaxation does not depend on the amount of administered relaxants. The relationship between Bolus-T_5 and the infusion rate of mivacurium was very strong. Therefore, the mivacurium infusion rate for an individual patient can be estimated from Bolus-T_5 and the appropriate regression equation. If a relaxogram, such as accelerograph or electromyelograph, is not available, T_5 is the time when the T1 is again palpable. Since the variation in individual infusion requirements is wide, Bolus-T_5 may be a useful indicator to titrate the infusion rate.[22]

In this study, the infusion rate of atracurium was not reduced in parturients. The physiologic changes during pregnancy or cesarean section have little effect on the metabolism of atracurium. The main metabolic pathway of atracurium is Hofmann elimination, which is a purely chemical reaction accelerated by alkaline pH and an increase in temperature. However, during cesarean sections or gynecological operations, body temperature was no different between the two types of operations and the pH changes during clinical practice probably had very little effect on the speed of metabolism. Some degree of enzymatic ester hydrolysis also probably occurred, but this enzyme system is not related to pChe and atracurium is not affected by pChe.[4,5]

The bolus dose of mivacurium was 0.15 mg/kg (200% of ED_{95}) whereas the bolus dose of atracurium was 0.15 mg/kg (60% of ED_{95}). As a result, complete muscle relaxation occurred by mivacurium bolus and Bolus-T_5 could be measured. However, when atracurium was used, we could not wait until relaxation by succinylcholine recovered fully because the onset time of atracurium is too long and might interfere with surgery. We had to inject a small amount of atracurium because a large bolus dose completely abolished twitch response throughout the cesarean section and we could not determine the infusion rate of atracurium. We found that the bolus dose of atracurium did not affect the subsequent infusion rate of atracurium if the infusion rate was measured after stabilization of twitch response by bolus dose of atracurium in a preliminary study.

In summary, the infusion rate of atracurium was not significantly different between the groups, but the infusion rate of mivacurium in parturients was significantly lower than in non-pregnant women while Bolus-T_5 in parturients was significantly longer than in non-pregnant women. There was no significant difference in the recovery indices between the 2 groups and there was little correlation between the infusion rate and the recovery indices of both relaxants, but there was a strong negative correlation between Bolus-T_5 and the infusion rate of mivacurium. We believe that the infusion rate of mivacurium in maintaining muscle relaxation in parturients should be reduced compared to the rate in non-pregnant women and that measuring Bolus-T_5 may be helpful in determining the infusion rate to maintain muscle relaxation.

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