Difference in the Effect of Pancuronium and Vecuronium on Baroreflex Control of Heart Rate in Humans

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The effects of pancuronium and vecuronium, each in doses of 0.05 and 0.08 $mg \cdot kg^{-1}$, on the baroreflex control of the heart rate were studied in 40 adult patients of either sex (21 men and 19 women) during stable nitrous oxide-oxygen-fentanyl anesthesia. The blood pressure was elevated by intravenous infusion of phenylephrine (4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) for the pressor test, and lowered by a bolus injection of nitroglycerin (0.3–0.5 mg) for the depressor test. Baroreflex sensitivity was judged from the slope of the regression of the systolic blood pressure on the succeeding R-R intervals on the ECG. There was no significant difference between the baseline blood pressure at which both tests were carried out. Nitrous oxide-oxygen-fentanyl anesthesia alone suppressed the baroreflex sensitivity to a level which was at the lower limit of the physiological and non-anesthetized state. The 0.08 $mg \cdot kg^{-1}$ dose of pancuronium significantly suppressed the reflex sensitivity in both the pressor and depressor tests. However, the 0.05 $mg \cdot kg^{-1}$ dose of pancuronium and both doses of vecuronium did not cause any significant change in the test results. (Key words: neuromuscular relaxant, pancuronium, vecuronium, reflexes, baroreceptor reflexes)

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It is relatively difficult to evaluate the influence of muscle relaxants on the autonomic nervous system in a clinical situation. For example, it is common to assess it by the changes in the blood pressure and heart rate after the administration of muscle relaxants[1–3], whereas the effects on the circulatory reflexes such as the baroreflex have rarely been studied. For the anesthetic management of patients with little circulatory reserve, muscle relaxants are frequently administered to supplement light general anesthesia in order to maintain circulatory homeostasis. If a muscle relaxant were to have a suppressive effect on the baroreflex function, it would be deleterious for patients whose baroreflex function is already aggravated. The aim of the present study was to examine the effects of clinical doses of two widely used muscle relaxants, pancuronium and vecuronium, on baroreflex control of the heart rate during light general anesthesia.

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Materials and Methods

Forty adult surgical patients (21 men and 19 women, aged 22–57, weighing 43–83 kg, ASA class I and free of neuromuscular disease) were studied with Ethical Committee approval and informed consent. They were premedicated with oral diazepam (10 mg)

Table 1. Patient age, awake arterial blood pressure and heart rate

	Age yr	SBP mmHg	DBP mmHg	HR bpm
Control	41 ± 3	113 ± 3	69 ± 3	72 ± 4
Pancuronium				
0.08 mg·kg^{-1}	37 ± 3	111 ± 5	67 ± 2	66 ± 4
0.05 mg·kg^{-1}	40 ± 4	109 ± 3	61 ± 3	72 ± 3
Vecuronium				
0.08 mg·kg^{-1}	36 ± 3	117 ± 4	72 ± 3	63 ± 2
0.05 mg·kg^{-1}	46 ± 3	116 ± 5	72 ± 4	71 ± 3

Data are means ± SEM. SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate

1.5 hours before induction of anesthesia and with deliberate exclusion of atropine. On their arrival in the operating room, each patient's blood pressure and heart rate were measured with an automatic blood pressure cuff (Nippon Kolin; Japan). An intravenous cannula was placed in a forearm vein. Continuous ECG (CM_5) monitoring was started, and two electrodes were attached to stimulate the ulnar nerve at the wrist. General anesthesia then was induced with thiamylal (5 mg·kg^{-1}), after which neuromuscular monitoring was started (Stimulator: Myotest MK II; Recorder: Myograph 2000; Biometer International; Denmark). Succinylcholine (1 mg·kg^{-1}) was administered for endotracheal intubation. Anesthesia was then maintained with intravenous fentanyl (2 μg·kg^{-1}) and nitrous oxide : oxygen (4L : 2L). The radial artery was cannulated for direct monitoring of the arterial blood pressure and collection of arterial blood samples for gas analysis (ABL III, Radiometer; Denmark). Ventilation was controlled to maintain normocapnia monitoring endtidal CO_2 analyzer (Normocap, Datex; Finland). When the depth of anesthesia was assessed as being too light from the heart rate and size of the pupils, additional doses of thiamylal (2 mg·kg^{-1}) and fentanyl (1 μg·kg^{-1}) were administered intravenously. After the twitch responses had returned to more than 70% of the control value (usually 5 to 10 min was needed after the injection of SCC), the patients were randomly divided into 5 groups of 8 subjects each according to the muscle relaxants administered: (1) control group: neither pancuronium nor vecuronium was administered; (2) and (3) pancuronium groups: 0.08 mg·kg^{-1} and 0.05 mg·kg^{-1}, intravenously; (4) and (5) vecuronium groups: 0.08 mg·kg^{-1} and 0.05 mg·kg^{-1}, intravenously.

Baroreflex control of the heart rate was evaluated using pressor and depressor tests. Phenylephrine was infused intravenously at a rate of 4 μg·kg^{-1}·min^{-1} for the pressor test and nitroglycerin was given by a bolus injection in a dose of 0.3–0.5 mg for the depressor test. The systolic blood pressure was elevated by approximately 30 to 40 mmHg during the pressor test, whereas it was lowered by 20 to 30 mmHg during the depressor test. In the control group, the pressor and depressor tests were performed after the hemodynamic parameters were stabilized. In the other groups, the tests were started 5 min after muscle relaxant injection in order to obtain sufficient neuromuscular blocking and a stable hemodynamic state.

The baroreflex sensitivity was assessed by evaluating the quantitative relationship between the systolic blood pressure and the succeeding R-R interval on the ECG. For each of the pressor and depressor tests, the relationship between the systolic blood pressure and the succeeding R-R interval was plotted on a beat-to-beat basis. The slope (msec·mmHg^{-1}), calculated by the least square method, was used as an index of the gain of baroreflex function[4,5].

Values are expressed as the mean ± SEM. Statistical analysis of the results was performed using analysis of variance (ANOVA) for multiple comparisons, and a P value of less than 0.05 was considered significant. If significant variance ratios were obtained using ANOVA, least significant differences were calculated by multiple comparison with Tukey's test.

Table 2. Systolic blood pressure (SBP) and heart rate (HR) before pressor or depressor test

	SBP mmHg	HR bpm
Control	101 ± 4	64 ± 2
Pancuronium		
0.08 mg·kg^{-1}	107 ± 2	73 ± 3
0.05 mg·kg^{-1}	92 ± 2	70 ± 2
Vecuronium		
0.08 mg·kg^{-1}	102 ± 5	53 ± 2*
0.05 mg·kg^{-1}	99 ± 4	60 ± 2**

Data are means ± SEM. *$P < 0.01$ vs both doses of pancuronium; **$P < 0.05$ vs 0.08 mg·kg^{-1} of pancuronium.

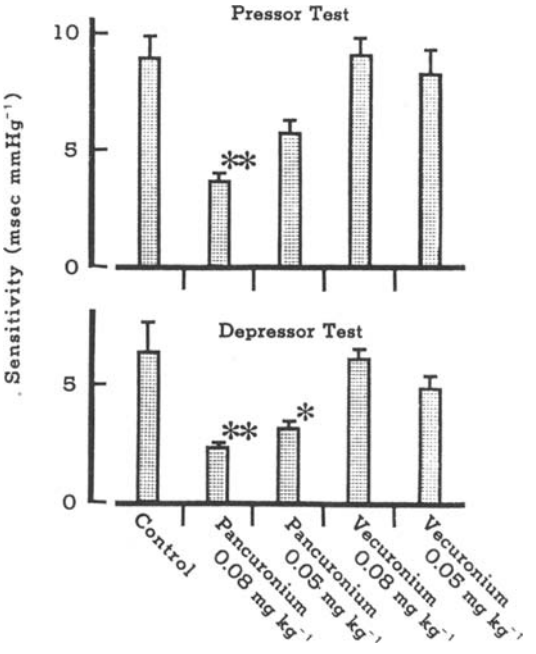

Fig. 1. Baroreflex responses after pressor (upper panel) and depressor test (lower panel). Data are means ± SEM. *$P < 0.05$, **$P < 0.01$ vs control value.

Results

The five groups of patients were comparable in terms of age, arterial blood pressure and heart rate in the awake state (table 1). During nitrous oxide-oxygen-fentanyl anesthesia, additional thiamylal and fentanyl were required in 3 patients in the control group and 2 patients in each of the other four groups. Supplemental anesthetic was administered once in each patient.

The systolic blood pressure did not differ significantly between the 5 groups just before the pressor or depressor test was initiated (table 2). The heart rate in both pancuronium groups was slightly higher and that in both vecuronium groups was slightly lower than in the control group, but the differences were not significant. Consequently, the systolic blood pressure and heart rate in both the pancuronium and vecuronium groups were not significantly different from those in the control group just before the pressor or depressor test.

All regression slopes had a correlation coefficient greater than 0.9 in the pressor and depressor tests. During the pressor test (fig. 1, upper panel), baroreflex sensitivity in the control group was 8.90 msec·mmHg^{-1} (mean). On the other hand, the sensitivities in the 0.08 and 0.05 mg·kg^{-1} pancuronium groups were 3.65 and 5.72, and those in 0.08 and 0.05 mg·kg^{-1} vecuronium groups were 9.00 and 8.27, respectively. Although the sensitivity in the pancuronium group was likely to decrease as the injected dose was increased, no significant dose-dependent difference was observed depending on the dose of the drug. The sensitivity in the 0.08 mg·kg^{-1} of pancuronium group was significantly less than that in the control and both vecuronium dosage groups.

Almost the same tendency was observed during the depressor test (fig. 1, lower panel). The sensitivity in the control group was 6.41 during the depressor test. The sensitivities in the 0.08 and 0.05 mg·kg^{-1} pancuronium groups were 2.32 and 3.14, and those in the 0.08 and 0.05 mg·kg^{-1} vecuronium groups were 6.11 and 4.86, respectively. Although no significant dose-dependent difference in sensitivity was detected with either drug, the sensitivity in the 0.08 mg·kg^{-1} pancuronium group was significantly less than that in the control and 0.08 mg·kg^{-1} vecuronium groups.

Discussion

While the baroreceptor reflex is one of the most important reflexes for maintaining circulatory homeostasis during anesthesia, it is suppressed by anesthetic agents and anesthetic techniques[6–9]. Impairment of the reflex has been shown to decrease the tolerance to hemorrhage[10] and possibly be responsible for fatal arrhythmias[11]. Baroreflex sensitivities in awake patients are reported to range from 8 to 20 msec·mmHg^{-1} [5,7]. During nitrous oxide-fentanyl anesthesia after thiamylal induction in the present study, the sensitivity of this reflex became 8.90 during the pressor test and 6.41 during the depressor test, which are at the lower limit of the sensitivities in awake subjects.

The doses of muscle relaxants we chose are commonly used during clinical anesthesia. The potency of vecuronium is reported to be equal to or slightly greater than that of pancuronium[12]. Therefore, the potency of 0.08 mg·kg^{-1} of pancuronium may be comparable to either 0.08 or 0.05 mg·kg^{-1} of vecuronium.

Our present study clearly showed that pancuronium depresses the baroreflex responses at a clinical dose, while vecuronium has little effect on it. This depression by pancuronium could be comparable to that of 1 MAC halothane or enflurane anesthesia[6,7]. It has been shown that baroreflex control of the heart rate is predominantly parasympathetic and diminishes with a decrease in parasympathetic tone[13]. Because pancuronium has weak vagolytic and sympathomimetic activities[14,15], pancuronium's effects on the baroreflex could be explained mostly by influences on the autonomic nervous system. Our results indicated that the effect of pancuronium on the baroreflex did not disappear even after the blood pressure and heart rate became similar to the control values where no nondepolarizing muscle relaxant was administered.

Based on the results of the present study, vecuronium is surmised to be preferable to pancuronium when baroreflex-depressing anesthetics such as volatile anesthetics are used. Vecuronium is also preferable for patients with congestive heart failure because the baroreflex function is already impaired in those patients[16]. On the other hand, pancuronium may be advantageous in the case of high-dose fentanyl anesthesia because the anesthesia causes severe bradycardia[12] due to enhancement of vagal efferent activity and augmentation of the baroreflex sensitivity in a dose-dependent manner[17].

In conclusion, baroreflex sensitivity during stable nitrous oxide-oxygen-fentanyl anesthesia was remarkably depressed by the intravenous injection of 0.08 mg·kg^{-1} of pancuronium. To the contrary, clinical doses of vecuronium had little effect on the reflex.

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