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Interactions of nicardipine to inhalation anesthetics sevoflurane and isoflurane

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Abstract: The hemodynamic effects and pharmacokinetics of nicardipine under general anesthesia were compared between two different volatile anesthetics, sevoflurane and isoflurane. Sixteen adult neurosurgery patients were divided into sevoflurane and isoflurane groups. Anesthesia was maintained with either sevoflurane or isoflurane (0.5–1.5%) and nitrous oxide in oxygen. When the blood pressure was stabilized [0.5 minimum alveolar concentration (MAC) in both anesthetics] during surgery, nicardipine 1 mg, i.v. was administered. Plasma catecholamines and nicardipine concentration were measured, and the pharmacokinetics of nicardipine were calculated. The decrease in blood pressure and the increase in heart rate 30 min after nicardipine administration were significant in the isoflurane group but not in the sevoflurane group. Although plasma catecholamine levels increased after nicardipine administration in the isoflurane group, no significant changes were observed in the sevoflurane group. The sevoflurane group had a significantly longer elimination half-life, a larger area under the plasma concentration curve, and smaller clearance of nicardipine compared to the isoflurane group. In summary, the effects of nicardipine on blood pressure and heart rate were significantly longer under isoflurane anesthesia than under sevoflurane anesthesia. However, the metabolism and excretion of nicardipine were significantly delayed under sevoflurane anesthesia.

Key words: Nicardipine, Pharmacokinetics, Hemodynamics, Sevoflurane, Isoflurane

Introduction

Nicardipine is a calcium antagonist used for perioperative blood pressure control, however the effects of nicardipine administered in general anesthesia may be modified because the anesthetic agent influences the pharmacokinetics of the agents. Although the effects of nicardipine administered under neuroleptanesthesia [1], halothane [2], enflurane [3], and isoflurane [4] anesthesia have been reported, there are few reports on the comparison of the effects of nicardipine between different anesthetics and on sevoflurane anesthesia. We have already reported that the hemodynamic effects and pharmacokinetics of nicardipine under enflurane anesthesia are different from those under isoflurane anesthesia [5]. In the present study, the hemodynamic effects and pharmacokinetics of nicardipine under sevoflurane anesthesia were compared with those under isoflurane anesthesia.

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Patients and methods

Sixteen patients without liver or renal diseases and who were ASA Class 1 or 2 for elective neurosurgery were investigated. They were randomly divided into two groups of eight potients each by the envelope method: sevoflurane group and isoflurane group.

We obtained written informed consent from each patient and institutional approval from the Ethics Committee of our hospital.

As premedication, atropine 0.01 mg·kg^{-1} and hydroxyzine 1 mg·kg^{-1} were injected intramuscularly 30 min before the patients arrived at the operating room. Anesthesia was induced with thiamylal 2 mg·kg^{-1}, midazolam 0.1 mg·kg^{-1}, and fentanyl 0.05 mg. Tracheal intubation was performed with vecuronium 0.15 mg·kg^{-1}. Anesthesia was maintained with either sevoflurane or isoflurane 0.5–1.5% (end-tidal concentration measured with an Ultima Datex, Helsinki, Finland), 3 l·min^{-1} of nitrous oxide in 2 l·min^{-1} of oxygen and fentanyl. Pancuronium was administered for neuromuscular blockade during surgery. End-tidal CO_2 concentration was adjusted to 30–35 mmHg by artificial ventilation. After the induction of anesthesia, a catheter was inserted into the dorsal pedal artery to measure blood pressure and to collect blood samples.

When the microsurgical procedure was started and blood pressure was stabilized, nicardipine 1 mg was

administered as a bolus. Blood pressure and the heart rate (by electrocardiogram) were measured immediately before and at 1, 3, 5, 10, 20, and 30 min after the nicardipine injection. Plasma epinephrine and norepinephrine levels were measured immediately before and at 5, 10, 20, and 30 min after the nicardipine injection with high-performance liquid chromatography (HPLC, NT detector, Yokohama Hewlett-Packard, Yokohama, Japan; detection limit 0.01 ng·ml^{-1}). The plasma nicardipine level was also measured at 5, 10, 20, and 30 min after the injection by HPLC (UV detector SPD-2A, Shimadzu, Hamamatsu Japan; detection limit 3 ng·ml^{-1}) [6]. The pharmacokinetics of nicardipine were approximated by the trapezoidal method. For 30 min before and after nicardipine administration, the concentrations of inhalational anesthetics and the infusion rate (2 ml·kg^{-1}·h^{-1}) were constant and no other drugs were administered.

All values are expressed as mean ± standard error. Statistical analysis consisted of the chi-square test for sex and kind of surgery, the Mann-Whitney U-test for other parameters between the two groups, and analysis of variance (ANOVA) with repeated measures followed by Student's *t*-test for blood pressure, heart rate, and plasma concentrations of nicardipine and catecholamines. The value $P < 0.05$ was considered statistically significant.

Results

The subjects' backgrounds, doses of fentanyl and muscle relaxants, and minimum alveolar concentrations (MACs) of sevoflurane and isoflurane at the time of nicardipine administration (2.05% was calculated as 1 MAC for sevoflurane and 1.15% for isoflurane) showed no significant differences between the two groups (Table 1). The nicardipine dose per kilogram of body weight was not different between the two groups (0.018 mg·kg^{-1}).

Table 1. Subjects' background

	Sevoflurane group	Isoflurane group
Number of patients	8	8
Sex (male/female)	5/3	4/4
Age (years)	60 ± 4	60 ± 4
Body weight (kg)	56.8 ± 3.0	55.4 ± 5.8
Kinds of surgery (Vascular/Tumor)	2/6	4/4
Duration of		
anesthesia (min)	598 ± 93	539 ± 88
surgery (min)	486 ± 95	434 ± 85
MAC at nicardipine injection	0.5 ± 0.04	0.5 ± 0.07
Time from start of anesthesia induction to nicardipine injection (min)	116 ± 4	118 ± 7
Dose of		
fentanyl (μg)	325 ± 19	383 ± 34
pancuronium (mg)	3.6 ± 1.0	4.0 ± 1.1

Mean ± SE.
MAC, minimum alveolar concentration.

Blood pressure and heart rate before nicardipine injection showed no significant differences between the two groups. Blood pressures that were significantly lower than preadministration levels continued for 30 min in the isoflurane group and for 20 min in the sevoflurane group. Although the heart rate measured 30 min after the administration still exceeded the preadministration value in the isoflurane group, those measured 10 min after the administration or later showed no differences from the preadministration value in the sevoflurane group (Fig. 1).

The plasma epinephrine and norepinephrine levels increased significantly after nicardipine administration in the isoflurane group while the sevoflurane group

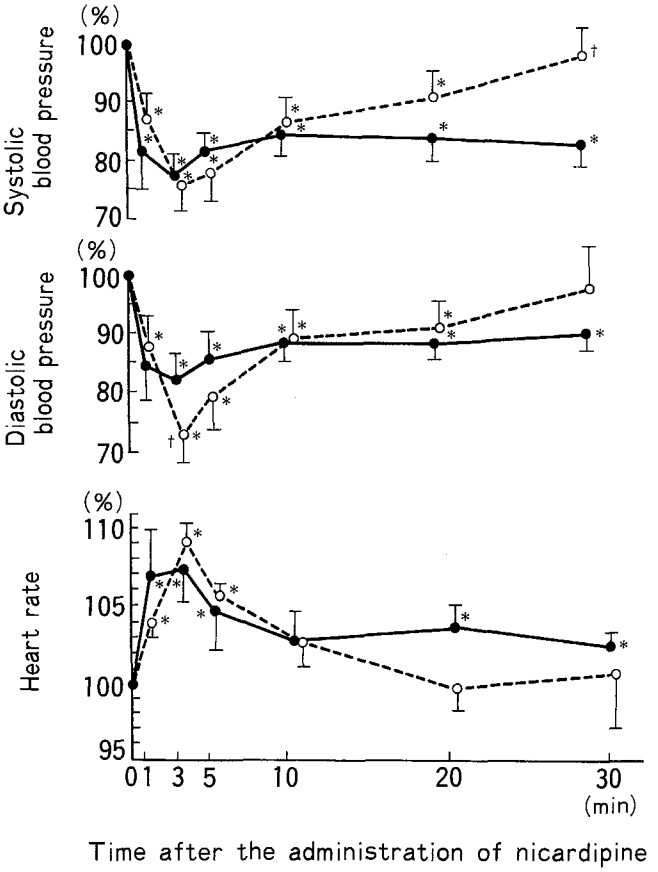

Fig. 1. Blood pressure and heart rate are shown as the percent change against the preadministration level (0 min). *Open circles* show the sevoflurane group ($n = 8$) and *closed circles* show the isoflurane group ($n = 8$). *Bars* indicate the standard errors. *$P < 0.05$ *vs* preadministration value; *$P < 0.05$ *vs* isoflurane group

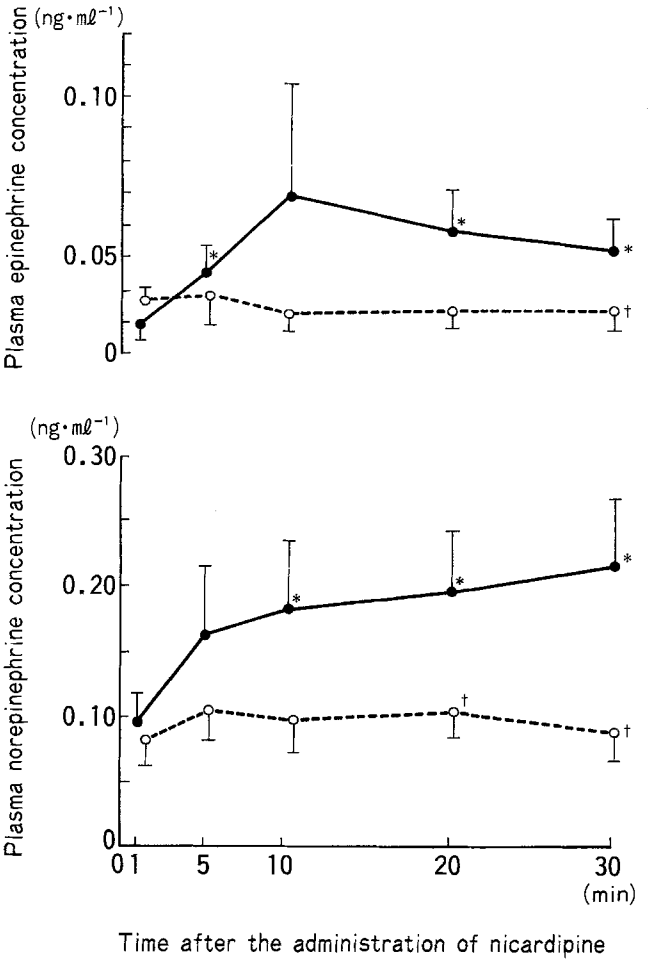

Fig. 2. Plasma catecholamine concentration *Open circles* show the sevoflurane group (n = 8) and closed circle shows the isoflurane group (n = 8). *Bars* indicate the standard errors. * $P < 0.05$ *vs* pre-administration value; *$P < 0.05$ *vs* isoflurane group

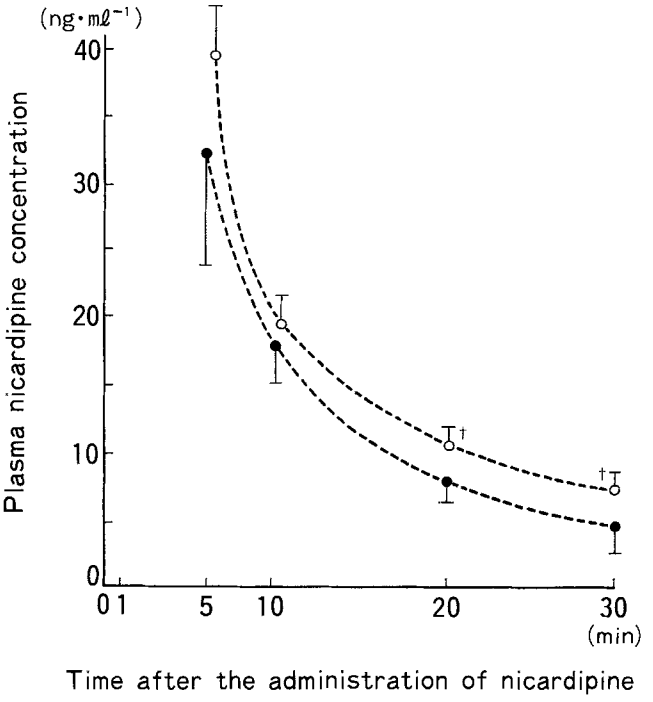

Fig. 3. Plasma nicardipine concentration. *Open circles* show the sevoflurane group (n = 8) and *closed circles* show the isoflurane group (n = 8). *Bars* indicate the standard errors. +$P < 0.05$ *vs* isoflurane group

showed no significant changes. Epinephrine and norepinephrine in the isoflurane group (epinephrine: 30 min after nicardipine injection; norepinephrine: 20 and 30 min after nicardipine injection) demonstrated significantly higher levels than those in the sevoflurane group (Fig. 2).

Plasma nicardipine concentrations in the sevoflurane group 20 and 30 min after nicardipine injection were significantly higher than those in the isoflurane group (Fig. 3). Compared with the isoflurane group, the sevoflurane group showed a longer elimination half-life ($T_{1/2\beta}$), a larger area under the plasma concentration curve (AUC), and lower clearance of nicardipine (Table 2).

Table 2. Pharmacokinetics of nicardipine

	Sevoflurane group	Isoflurane group
$T_{1/2\beta}$ (min)	28.0 ± 6.8*	13.2 ± 3.0
AUC (ng·min·ml^{-1})	1110 ± 108*	603 ± 130
Cl (l·min^{-1})	1.0 ± 0.1*	2.2 ± 0.5

Mean ± SE.
$T_{1/2\beta}$, elimination half-life; AUC, area under the plasma concentration curve; Cl, total clearance.
*$P < 0.05$ *vs* isoflurane group.

Discussion

The important findings in this study were that the effects of nicardipine on hemodynamics were significantly longer under isoflurane anesthesia than those under sevoflurane anesthesia, but the metabolism and excretion of nicardipine were significantly delayed under sevoflurane anesthesia.

Except as reported by Kishi et al. [1], nicardipine increased heart rate, as shown in the present study, by reflex sympathetic hypertonia due to hypotension under general anesthesia [2,5,7,8]. The results reported by Kishi et al. and by others might differ as a result of the effects of surgical stress, because Kishi et al. administered nicardipine when hypertension occurred by surgical stress. Therefore, we studied the changes during microscopic procedure in neurosurgery to minimize the influence of surgical stress in the present study.

Enflurane was reported to enhance the cardio-vascular depression by verapamil more significantly than halothane [9] and isoflurane [10]. Regarding the effects

of nicardipine, we demonstrated that isoflurane enhanced the hemodynamic effects more significantly than enflurane [5].

The effects of isoflurane on hemodynamics were reported to be the same as those of sevoflurane[11]; however, the results of our study suggested that isoflurane had stronger effects than sevoflurane in accelerating hypotension and reflex sympathetic hypertonia by nicardipine. In the present study, the comparison between the two groups was not affected by fentanyl because the same amount of fentanyl was administered to the two groups before the study, and for 30 min each before and after the nicardipine injection fentanyl was not administered. Therefore, the different effects were due to the interaction of inhalational anesthetics and nicardipine.

The larger $T_{1/2\beta}$ and AUC of nicardipine and the smaller clearance of nicardipine in sevoflurane anesthesia than in isoflurane anesthesia was thought to be due to decreased blood flow or decreased liver function. Although Frink et al. [12] and Bernard et al. [13] reported that the effects of sevoflurane and isoflurane on hepatic blood flow were similar, Fujita et al. [14] demonstrated that sevoflurane decreased portal blood flow more significantly than isoflurane. In the present study, the decreases in blood pressure and catecholamine release were greater in the isoflurane group than in the sevoflurane group, while the metabolism of nicardipine was faster in the isoflurane group. This may have been because the decrease in hepatic blood flow or liver function under sevoflurane anesthesia was larger than those induced by decreased blood pressure and increased catecholamine release under isoflurane anesthesia.

In summary, hypotension and reflex sympathetic hypertonia induced by nicardipine were enhanced and prolonged significantly under isoflurane anesthesia compared with sevoflurane anesthesia; however, the metabolism and excretion of nicardipine was significantly slower under sevoflurane anesthesia than under isoflurane anesthesia.

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