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Pharmacokinetics of ketamine during hypothermic cardiopulmonary bypass in cardiac patients

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Abstract: Cardiopulmonary bypass (CPB) makes prediction of any drug concentration difficult because both hypothermia and hemodilution can alter the pharmacokinetics of the drug. Eleven patients undergoing cardiac surgery under CPB were anesthetized with continuous infusion of ketamine combined with intermittent administration of droperidol and fentanyl. The infusion rate of ketamine was 2 $mg \cdot kg^{-1} \cdot hr^{-1}$ following a bolus administration of 1.5 $mg \cdot kg^{-1}$ for the induction of anesthesia. Blood concentrations of ketamine and its main metabolite, norketamine, were measured at 0, 30, and 60 min after the start of and the end of CPB, and 0, 1, 2, and 24 h after the cessation of ketamine infusion. Hypothermia increased blood ketamine levels during CPB, but the norketamine levels did not change. Although acute hemodilution would decrease blood ketamine levels, their levels were already significantly increased at 30 min after CPB. Hypothermic factors have a more kinetically important role during CPB than hemodilution. Increases in blood norketamine levels following rewarming indicate that hypothermia could impair ketamine metabolism in the liver. Further increase in the plasma concentration of ketamine until 30 min after the end of CPB might be due to blood transfusion containing ketamine from the CPB reservoir.

Key words: Total intravenous anesthesia, Ketamine, Pharmacokinetics, Cardiopulmonary bypass, Hypothermia

Introduction

Ketamine has been applied for cardiac anesthesia since 1970 [1]. The pharmacokinetics of ketamine during cardiopulmonary bypass (CPB), however, remain unknown.

Both hypothermia and hemodilution during CPB markedly alter the drug pharmacokinetics. Although hemodilution decreases the blood concentration of any drug, hypothermia reduces clearance of the drug dependent on hepatic metabolism [2]. As ketamine is metabolized in the liver, its pharmacokinetics will be altered by hypothermic CPB. Therefore, the prediction of blood levels of ketamine could be difficult during hypothermic CPB, particularly in the beginning of CPB.

We determined the influence of hypothermic CPB on the pharmacokinetics of ketamine under total intravenous anesthesia with ketamine, droperidol, and fentanyl in patients undergoing cardiac surgery.

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Materials and methods

Patients

After the approval of our study by the institutional ethical committee, 11 patients scheduled to undergo elective cardiac surgery under hypothermic CPB were the subjects of the study. Informed consent was obtained from each patient.

Seven patients underwent aortocoronary artery bypass: two patients for mitral valve replacement with tricuspidal valvuloplasty, one patient for aortic valve replacement, and one patient for left ventricular aneurysmectomy.

Anesthesia

All patients were premedicated with diazepam 10 mg p.o. and roxatidine 75 mg p.o. 90 min before arrival in the operating room and with intramuscular morphine 5 mg 30 min before arrival.

Anesthesia was induced with fentanyl 5–10 $\mu g \cdot kg^{-1}$ and ketamine 1.5 $mg \cdot kg^{-1}$, and maintained with continuous infusion of ketamine at a rate of 2 $mg \cdot kg^{-1} \cdot hr^{-1}$. Total doses of fentanyl 30 $\mu g \cdot kg^{-1}$ and droperidol 0.25 $mg \cdot kg^{-1}$ were also combined.

Tracheal intubation was facilitated with vecuronium 0.1 mg·kg^{-1} followed by mechanical ventilation with oxygen in air to maintain PaO_2 at 100–200 mmHg. Vecuronium was incrementally administered as a muscle relaxant when needed. At the end of surgery, ketamine infusion was stopped. Esophageal temperature was kept between 26°C and 28°C during CPB.

Prostaglandin E_1 (PGE_1), was continuously infused at 10–20 ng·kg^{-1}·min^{-1} to maintain good peripheral circulation. Isosorbide dinitrate as a coronary dilator was also continuously administered at 0.5 μg·kg^{-1}·min^{-1}. Urinastatin 300 000 units and methyl predonisolone 1.5 g were given during CPB. Catecholamines were infused to wean from CPB if necessary.

Blood sampling

Arterial blood samples were collected on the following occasions to measure hematocrit (Ht), plasma total protein (TP), pH, and plasma concentrations of ketamine and norketamine: 0, 30, and 60 min after the initiation and termination of CPB, and 0, 1, 2, and 24 h after the end of ketamine infusion. The samples taken were centrifuged immediately and the plasma was stored at −20°C until measurement.

Plasma concentrations of ketamine and norketamine were determined by gas chromatography mass spectrometry as reported previously [3]. Then blood levels of ketamine and norketamine were calculated from the plasma level and Ht.

Statistical analysis

All values obtained are expressed as mean ± SD. Data were statistically analyzed with repeated measurements ANOVA followed by Fisher's PLSD test. $P > 0.05$ was considered significant.

Results

Arterial blood pH and plasma TP

Although pH from just before the stop of CPB to 2 h after cessation of ketamine infusion was significantly lower than the pH at just before the start of CPB (Table 1), the pH did not decrease below 7.30 in any of the patients during the study. TP significantly decreased to 56% during CPB compared with the pre-CPB value.

Blood concentration of ketamine

The blood concentration of ketamine just before the start of CPB was 0.57 ± 0.22 μg·ml^{-1} (Fig. 1). Hypothermic CPB increased the level gradually up to 1.05 ± 0.29 μg·ml^{-1} at 30 min after the termination of CPB. It decreased to 48% and 33% at 1 and 2 h after the stop of ketamine infusion, respectively, as compared with the level at the end of ketamine infusion. It could not be detected 24 h after the end of anesthesia.

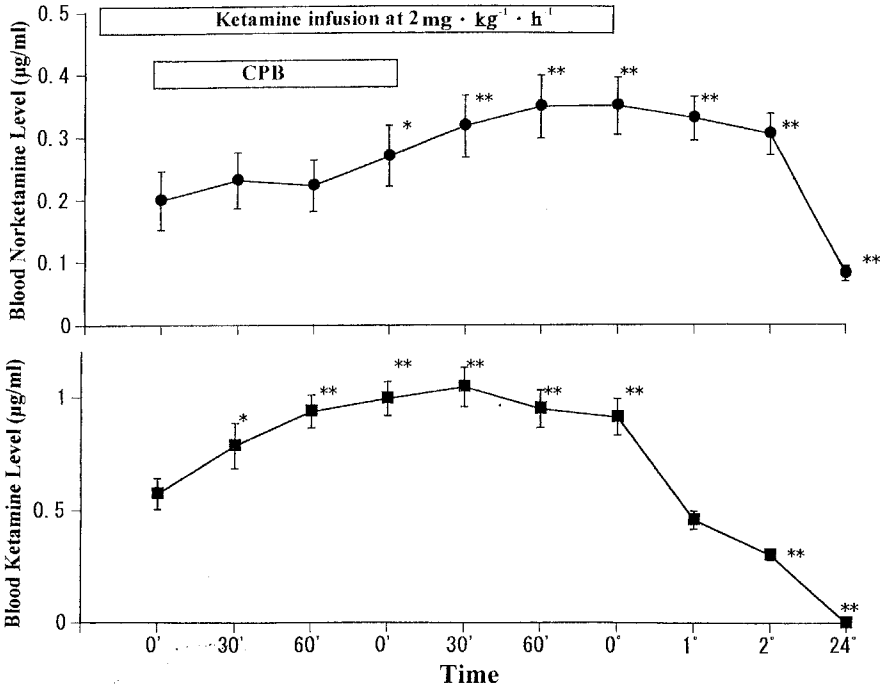

Fig. 1. Changes in blood concentrations of ketamine and norketamine. The results are expressed as mean ± SEM. *Closed squares*, blood level of ketamine *closed circles*, blood level of norketamine. 0′: 0 min, 0°: 0 h CPB, cardiopulmonary by pass

Table 1. Changes in pH and total protein

	CPB			Post-CPB			Ketamine off			
	0′	30′	60′	0′	30′	60′	0°	1°	2°	24°
pH	7.41 ±0.05	7.41 ±0.05	7.39 ±0.07	7.43 ±0.05	7.34** ±0.04	7.34** ±0.04	7.36** ±0.05	7.36 ±0.04	7.36 ±0.05	7.39 ±0.05
TP	6.0 ±0.9	3.4** ±0.4	3.8** ±0.5	4.5** ±0.5	5.0** ±0.8	5.3** ±0.7	5.4** ±0.7	5.5* ±0.7	5.7 ±0.5	6.4 ±0.4

* $P < 0.05$, ** $P < 0.01$ compared to CPB 0′, Mean ± 0 SD.
TP, total protein (g/dl); CPB, cardiopulmonary bypass; Post-CPB, after termination of CPB; Ketamine off, after stop of ketamine infusion.

Blood concentration of norketamine

The blood concentrations of norketamine changed little until 1 h after the start of CPB (Fig. 1). Thereafter, it increased gradually until the stop of ketamine infusion. It decreased to 94%, 87%, and 23% at 1, 2, and 24 h after the stop of ketamine infusion, respectively, compared to the concentration at the end of ketamine infusion.

Discussion

Knowledge of the pharmacokinetics of the main anesthetics in total intravenous anesthesia is of particular importance in the management of surgical patients. Hypothermic CPB causes an appreciable alteration of the pharmacokinetics of any drug. Hemodilution and hypothermia are the two most important events in this respect [2]. Hypothermia reduces the rate of metabolism of the drugs because it decreases the effective hepatic blood flow with intrahepatic blood shunting and decreases the activity of hepatic microsomal enzymes [2]. The initiation of CPB is accompanied by the rapid infusion of 1.5–2.0 l of pump-priming solution. This event will cause a rapid decrease in the blood concentration of drugs. Thus, predicting the blood concentration of ketamine may be difficult.

During CPB, we infused ketamine at the same rate of 2 $mg \cdot kg^{-1} \cdot h^{-1}$ as in the pre-CPB, and measured the blood concentrations during and after the CPB. The changes in the blood concentrations of ketamine during CPB were similar to the changes in blood propofol levels during CPB as reported by Russell et al. [4].

The ketamine level already increased to 137% of the pre-CPB value at 30 min after the start of CPB, suggesting that hypothermia between 26°C and 28°C accounted for a greater proportion of the significant increase in blood ketamine concentrations during CPB than hemodilution did. Although the blood norketamine concentration did not change during hypothermia, it increased during the rewarming period. Thus, hepatic metabolism of ketamine may be appreciably impaired by hypothermia and rapidly improved by rewarming.

The blood ketamine concentrations increased continuously even after rewarming and until 30 min after the termination of CPB. This increase could result from an infusion of the residual blood containing ketamine from the pump reservoir, and Russell et al. [4] reported similar data for propofol anesthesia. On the other hand, as the disappearance rate of ketamine in the blood after the stop of ketamine infusion was slower than reported previously by Matsuki et al. [5] and Idvall et al. [6], hepatic metabolism might not yet be completely recovered even after the anesthesia. However, the plasma concentration of ketamine 1 h after the cessation of ketamine infusion (0.55 ± 0.16 $\mu g \cdot ml^{-1}$) was lower than the emergence concentration (0.7 $\mu g \cdot ml^{-1}$) [7].

We continuously infused PGE_1 to maintain good peripheral circulation. The infusion might reduce blood ketamine concentrations during hypothermic CPB because PGE_1 is reported to increase hepatic flow [8,9] and attenuate the decrease in hepatic cell function during hypotension [10,11]. Therefore, if we had not used PGE_1, the ketamine level might have been higher.

Although plasma TP level was significantly reduced from 6.0 ± 0.9 to 3.5 ± 0.4 $g \cdot dl^{-1}$ with initiation of CPB, its changes might not greatly affect the depth of anesthesia because ketamine does not bind significantly to plasma proteins [12].

The blood pH levels decreased significantly during hypothermic CPB. However, as the level was always more than 7.30 in all patients, the dissociation constant of ketamine was not significantly affected.

These results indicate that perhaps the infusion rate of ketamine should be reduced during hypothermic CPB to 1.0–1.5 $mg \cdot kg^{-1} \cdot hr^{-1}$ to obtain more stable levels of blood ketamine.

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