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·kg\(^{-1}\)·hr\(^{-1}\) following a bolus administration of 1.5 mg·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.

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 µg·kg\(^{-1}\) and ketamine 1.5 mg·kg\(^{-1}\), and maintained with continuous infusion of ketamine at a rate of 2 mg·kg\(^{-1}\)·hr\(^{-1}\). Total doses of fentanyl 30 µg·kg\(^{-1}\) and droperidol 0.25 mg·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\(^{-1}\). Urokinase 300,000 units and methyl prednisolone 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.