—Report on Experiments and Clinical Cases—

Blood Concentration of Propofol in a Patient with Delayed Emergence from Propofol-nitrous Oxide Anesthesia

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Abstract

We measured the blood concentration of propofol in a patient with delayed emergence from propofol-nitrous oxide anesthesia. A 78-year-old man underwent subtotal gastrectomy under both epidural and propofol-nitrous oxide anesthesia and did not regain consciousness soon after termination of propofol infusion. Preoperative laboratory examination revealed anemia and a low blood total protein concentration, but there was no evidence of impaired liver function. While the anesthesiologists were waiting for the patient to regain consciousness, a surgeon mentioned that the common hepatic artery might have been occluded during surgical manipulation. Arterial blood samples were obtained 50 and 80 minutes after termination of propofol infusion, and the blood concentration of propofol was measured. We considered that clearance of propofol through the hepatic route may have been impaired; however, the actual blood concentrations of propofol were not significantly increased compared with the respective blood concentrations obtained in the simulation. Therefore, the acute liver damage did not significantly impair elimination of propofol. Because most propofol molecules in the blood bind to proteins and erythrocytes, it is suspected that the anemia and low blood total protein concentration led to an increase in the free fraction of propofol in the blood, thereby delaying emergence from anesthesia.

(J Nippon Med Sch 2005; 72: 300–303)

Key words: propofol, blood concentration, delayed emergence

Introduction

Propofol, an intravenous anesthetic, is widely used for both induction and maintenance of general anesthesia. It is a short-acting drug with a large volume of distribution and high total body clearance. Although propofol is mainly eliminated through the hepatic route, extrahepatic clearance of propofol has been suggested to play a role[1,2]. Delayed recovery from propofol anesthesia has been reported in patients with liver dysfunction or liver cirrhosis[3,4], and the Food and Drug Administration of the U.S. and the pharmaceutical company (Astra Zeneca, London, UK) that manufactures propofol issued a worning about the possibility of delayed emergence from propofol anesthesia. However, the blood concentration of propofol during delayed emergence from propofol anesthesia has not been measured. We measured the blood concentration of propofol in a patient with delayed recovery from propofol-nitrous oxide anesthesia.

Case Report

A 78-year-old man (height, 171 cm, and weight,

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Table 1 Laboratory data before and after the surgery

	Before surgery	Postoperative day 1
LDH (IU/*l*)	380	674
ALT (IU/*l*)	31	749
AST (IU/*l*)	39	628
cholinesterase (IU/*l*)	190	120
total protein (g/d*l*)	7.3	4.9
albumin (g/d*l*)	3.9	2.4
total bilirubin (mg/d*l*)	0.28	0.40
ICG clearance rate (min^{-1})	0.168	0.105 *

Normal ranges are as follows: LDH, 180 ～ 460IU/*l*; ALT, 5 ～ 40 IU/*l*; AST, 10 ～ 35 IU/*l*; Cholinesterase, 185 ～ 431 IU/*l*; Total protein, 6.7 ～ 8.3g/d*l*; Albumin, 3.8 ～ 5.3 g/d*l*; Total bilirubin, 0.22 ～ 1.00 g/d*l*; ICG clearance rate, 0.158 ～ 0.232min^{-1}.
* The ICG clearance rate was measured immediately after surgery with a pulse dye densitometer.

57 kg) with cancer of the stomach was admitted to our hospital, and elective subtotal gastrectomy was scheduled. Preoperative laboratory examination revealed anemia with a hemoglobin (Hb) concentration of 10.4 g/d*l* and a hematocrit (Hct) of 34.4%, but there was no evidence of impaired liver function (**Table 1**). Premedication was not administered before anesthesia. In the operating room, an epidural catheter was placed through the thoracic 11/12 interspace, and 2% mepivacaine, 6 m*l*, was injected through the epidural catheter. Fifteen minutes later, cold analgesia between Th 4-L3 was confirmed using an alcohol pad. General anesthesia was induced by intravenous (i.v.) bolus administration of 60 mg propofol, and i.v. administration of 8 mg vecuronium facilitated tracheal intubation. Anesthesia was maintained by continuous i.v. infusion of propofol at an initial rate of 5 $mgkg^{-1}hr^{-1}$, with a mixture of 35% oxygen and nitrous oxide, as well as incremental epidural injection of mepivacaine. Opioids were not administered at any time during the surgery. Monitoring included 3-lead electrocardiography, invasive and noninvasive monitoring of arterial blood pressure, and measurement of end-tidal CO_2, SpO_2, and rectal temperature. The rate of propofol infusion was 5 $mgkg^{-1}hr^{-1}$ during the first 110 min of the surgery, 3 $mgkg^{-1}hr^{-1}$ during the next 73 min, and 2 $mgkg^{-1}hr^{-1}$ during the next 116 min. Propofol infusion was terminated at the beginning of skin closure. As soon as the patient began breathing spontaneously, muscle relaxation was reversed with i.v. administration of 1.0 mg atropine and 2.0 mg neostigmine. The operative time from incision to skin closure was 5 hours, and the amount of blood loss was 500 m*l*. The total amount of propofol infused was 1,083 mg. Arterial blood gas analysis, which was performed while the patient was receiving the nitrous oxide mixture at the end of surgery, showed the following values: PaCO2, 44 mmHg; PaO_2, 199 mmHg; Hb, 9.3 g/d*l*; Hct, 33.2%; and base excess, −2.9. Although we called the patient's name and gently shook him, he did not regain consciousness. Rectal temperature was 36.3°C. While waiting for the patient to regain consciousness, one of the surgeons mentioned that they might have occluded the common hepatic artery to control bleeding during surgical manipulation. Thus, we initially suspected that the reason for the prolonged unconsciousness was delayed elimination of propofol. We obtained arterial blood samples (3 m*l* each) 50 min and 80 min after termination of propofol infusion, and measured the blood concentration of propofol. After confirming that the patient had regained sufficient pharyngeal reflex and spontaneous ventilation, the patient was extubated. In the surgical ward, the patient did not respond to verbal commands. We examined the indocyanine green (ICG) clearance rate using a pulse dye densitometer (DDG-2001, Nihon Koden, Tokyo, Japan). The ICG clearance rate (k) was markedly low at 0.105 (normal range, 0.158～0.232). Compared

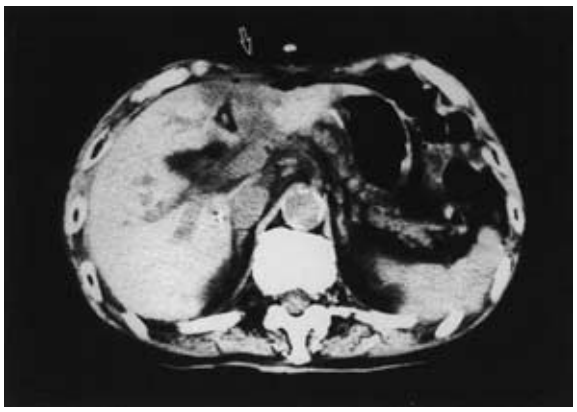

Fig. 1 Computed tomography of the liver performed on postoperative day 2. **Arrow** indicates segmental necrosis of the liver. There had been no evidence of impaired liver function before the operation. One of the surgeons mentioned that they may have injured the common hepatic artery during surgical manipulation. However, the blood concentrations of propofol 50 min and 80 min after termination of propofol infusion were not significantly increased compared with the respective values obtained in the simulation, indicating that hepatic clearance of propofol was not significantly impaired.

with the ICG clearance rate before the surgery (k = 0.168), there was an approximately 40% reduction in the ICG clearance rate (**Table 1**). The patient regained consciousness and responded to verbal commands 5 hours after termination of propofol infusion. Laboratory examination on postoperative day 1 revealed impaired liver function (**Table 1**). Computed tomography revealed segmental necrosis of the liver (**Fig. 1**). In the blood samples obtained 50 min and 80 min after termination of propofol infusion, the blood concentrations of propofol as measured with high-performance liquid chromatography were 0.623 μg/m*l* and 0.583 μg/m*l*, respectively. We traced the dose of propofol infused during the surgery, and used the Stanpump program (Steven L. Shefer, MD, Department of Anesthesiology, Stanford University, Palo Alto, CA) and Marsh's formula to obtain simulated values of the blood concentration of propofol. The predicted blood concentrations of propofol 50 min and 80 min after termination of propofol infusion were 0.36 μg/m*l* and 0.28 μg/m*l*, respectively.

Discussion

We present a case of delayed recovery from propofol-nitrous oxide anesthesia. Although our patient was anemic both before and after anesthesia, the core temperature was maintained at the time of emergence. Early recovery of spontaneous ventilation rules out the possibility that the muscle relaxants were responsible for the delayed emergence. Whether propofol is administered as a bolus or by continuous infusion, it is distributed to fat and muscle tissues and is rapidly metabolized via the hepatic and, possibly, extrahepatic routes[1,2]. In the present case, a surgeon mentioned that the common hepatic artery may have been occluded during the surgery, and we initially suspected that the reason for delayed emergence was delayed elimination of propofol. The infusion rate of propofol during the anesthesia was not excessively high[5]. In our patient, the actual blood concentrations of propofol at 50 min and 80 min after termination of propofol administration were not significantly increased compared with the respective values obtained in the simulation. In the present case, despite acute liver damage that reduced the ICG clearance rate, the rate of elimination of propofol was maintained at nearly the same level. These results are consistent with the pharmacokinetics of propofol in patients with cirrhosis[6,7]. Takizawa et al. [8] have demonstrated that the kidneys play a role in the elimination of propofol and that renal clearance of propofol comprises approximately 27% of the total body clearance of propofol. In our patient, renal clearance of propofol might have contributed to the reduction in the blood concentration of propofol.

Previously reported patients with delayed emergence from propofol anesthesia had had impaired liver function and a reduced ICG elimination rate before the surgery[3,4]. Upon a single injection or infusion of propofol in patients with mild-to-moderate liver cirrhosis, the elimination of propofol was not reduced compared with that in patients with normal liver function[6,7]. In patients who received long-term administration of propofol for anesthesia during long surgeries, the blood

concentration of propofol upon awakening was nearly 1 μg ml^{-1}[9]. In our patient, the blood concentration of propofol 50 min after termination of propofol administration was 0.623 μg ml^{-1}, which was sufficiently low for the patient to regain consciousness; however, our patient did not regain consciousness until 5 hr after termination of propofol infusion. Most studies that have reported the awakening blood concentration of propofol involved subjects who did not undergo surgical manipulation and therefore did not have blood loss[9]. The precise reason for delayed emergence from propofol anesthesia in our patient is not known. The measured blood concentration and the estimated blood concentration in this patient are whole-blood concentrations including erythrocytes or proteins binding propofol. One possible reason for delayed emergence is that the patient was anemic (Hb = 9.3) and had a low blood total protein concentration, as seen in the laboratory data on postoperative day 1. It has been reported that more than 90% of propofol molecules in the blood bind to proteins and erythrocytes[7,10]. An increase in the unbound fraction of propofol induced by acute hemodilution by cardiopulmonary bypass increases the anesthetic action of propofol[11]. In the present case, the total blood protein concentration and the hemoglobin concentration had decreased owing to bleeding and hemodilution. The reduced blood total protein concentration may have resulted in an acute increase in the free fraction of propofol, which may in turn have delayed the emergence of our patient from propofol anesthesia. However, the decreases in hemoglobin concentration and total protein concentration were not severe. Although reduced total protein concentration and anemia might have caused the delayed emergence, other possible causes remain.

In summary, we have presented a case of unexpected delayed recovery from propofol-nitrous oxide anesthesia in a patient with acute liver damage during surgery. However, the acute liver damage in this case did not significantly reduce the elimination rate of propofol. Although the precise reason for delayed emergence from propofol anesthesia in this case is not known, it is suspected that the anemia and low blood total protein concentration increased the free fraction of propofol in the blood, thereby delaying emergence from anesthesia.

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(Received, May 31, 2005)
(Accepted, June 29, 2005)