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Propofol pharmacokinetics in a patient with bilateral leg amputation

Tsunehisa Tsubokawa, Keisuke Ohta, Katsumi Tashiro, Shigeo Ohmura, and Ken Yamamoto

Department of Anesthesiology and Intensive Care Medicine, School of Medicine, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8641, Japan

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Propofol is one of the commonly used anesthetics, but awareness during propofol anesthesia remains a rare but clinically serious problem. The incidence of awareness is reported to be less than 0.5% [1,2]; however, it sometimes causes serious psychological sequelae, including sleep disturbance. To avoid this complication, pharmacokinetic information is important for the control of propofol dosage. Because the pump used for propofol infusion requires only the patient's weight as input, it is especially difficult to apply to patients with extreme body types, such as severely obese or emaciated patients. We have experience of a patient who undernent bilateral leg amputations who claimed awareness during propofol anesthesia. We considered that the cause of awareness was the shortness of propofol dosage, because we had infused propofol based on the patient's measured weight. To clarify whether propofol dosage based on the measured weight is insufficient, we investigated propofol pharmacokinetics in another patient undergoing leg amputation.

An 84-year-old man with arteriosclerosis obliterans was scheduled for an additional amputation of his right leg, which had been already amputated below the knee joint. This study was approved by the clinical research ethics committee of our university. The patient gave written consent to sampling of blood for measurements of propofol concentration. His left leg had been amputated at 10 cm below the hip joint. His measured weight was 40 kg. When his legs were intact, his weight was 55 kg according to clinical notes. In this case, we had input 55 kg as his weight (termed the "hypothetical weight") to the infusion pump for propofol.

Without premedication, anesthesia was induced with 50 μg of fentanyl and 80 mg of propofol intravenously. Before induction of anesthesia, an indwelling catheter was inserted into the left radial artery for blood sampling. A laryngeal mask airway was inserted without the use of muscle relaxants. Propofol was first infused at a rate of 10 $mg \cdot kg^{-1} \cdot h^{-1}$ based on the hypothetical weight, and the infusion rate was controlled between 5 and 10 $mg \cdot kg^{-1} \cdot h^{-1}$ according to clinical signs. During the operation, the patient's blood pressure and heart rate were stable, his pupils were contracted, and no spontaneous movement was observed. The operation lasted 60 min, and propofol infusion was stopped (propofol was infused for 70 min). About 10 min after the termination of propofol, he regained consciousness.

In order to investigate the pharmacokinetics of propofol, 18 arterial blood samples (1.0 ml each) were appropriately obtained for 240 min after the start of propofol infusion. The propofol concentration was determined by using high-performance liquid chromatography, as described by Plummer [3]. The data were pharmacokinetically analyzed with NONMEM (GloboMax, Hanover, MD, USA) and are shown in Table 1 together with normal human adult values calculated by the parameter set by Marsh et al. [4].

Figure 1 shows the measured propofol concentrations, the curve fitted by NONMEM, and the simulation result of propofol concentrations based on the measured weight ["The patient (40 kg)" in Table 1]. In the figure, propofol concentration can be kept high enough ($>3\ \mu g \cdot ml^{-1}$) [5] when propofol is infused based on the hypothetical weight, whereas it fails in the case when the measured weight is chosen as the input of the propofol infusion pump.

In this case, we infused propofol based on the hypothetical weight, assuming that the patient had both legs intact. As a result, the propofol concentration was kept

Address correspondence to: T. Tsubokawa
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Table 1. Pharmacokinetic parameters

Parameter	Normal patient (55 kg)	Normal patient (40 kg)	The patient (40 kg)
V_1 (l)	12.54	9.12	13.14
V_2 (l)	25.54	18.57	9.52
V_3 (l)	159.22	115.80	150.36
CL_1 ($l \cdot min^{-1}$)	1.49	1.09	1.19
CL_2 ($l \cdot min^{-1}$)	1.40	1.02	1.29
CL_3 ($l \cdot min^{-1}$)	0.52	0.38	0.56

V_1, V_2, and V_3 are the volumes of the central, shallow, and deep compartments, respectively. CL_1, CL_2, and CL_3 are the elimination clearance, the intercompartment clearance between the central and shallow compartments, and the intercompartment clearance between the central and deep compartments, respectively. Parameters "for normal patient" are calculated based on the parameter set of Marsh et al. [4]

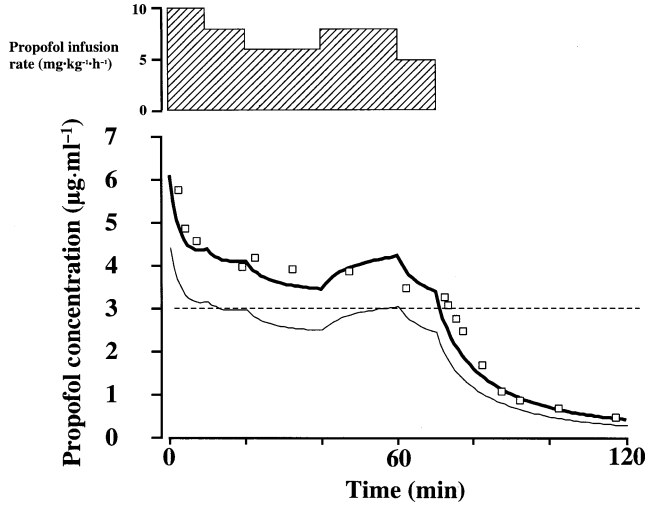

Fig. 1. Results of the simulation study and measured propofol concentrations. *Open squares*, measured propofol concentrations; *thick line*, fitting curve calculated by NONMEM; *thin line*, results of simulation study in cases when propofol is infused based on the measured weight (40 kg). The parameters for simulation studies were obtained by pharmacokinetic analysis of the patient data using NONMEM

above the necessary level during anesthesia, and the patient never regained consciousness during the operation (according to the postoperative interview). There were no clinical signs of overdose or underdose of propofol.

The reason that the measured weight is not suitable for the input of the propofol infusion pump is probably that the physical composition of a patient with an amputated leg is different from that of a normal patient. In a patient with amputated legs, the original size of the visceral organs is maintained, including the liver, a main site of propofol metabolism; therefore, propofol clearance does not change when the leg is lost. The central compartment containing vessel-rich organs may not show sigunificant change, either. Accordingly, patients with amputated legs maintain the original clearance and central compartment volume after amputation, which means that they have a larger clearance and a larger distribution volume of the central compartment relative to their measured weight.

In conclusion, when propofol is used to anesthetize leg-amputated patients, the dosage should be determined according to the hypothetical weight based on the assumption of intact legs.

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