Pharmacokinetics of Propofol in Elderly Coronary Artery Bypass Graft Patients under Total Intravenous Anesthesia

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The present paper investigates the pharmacokinetics of propofol in the plasma of two elderly patients operated on under total intravenous anaesthesia using propofol. A 78-year-old (patient A) and a 76-year-old (patient B), both Japanese men with unstable angina pectoris, were operated on for coronary artery bypass grafts. For the induction of anesthesia, 1.5 mg/kg propofol was administered as a single bolus infusion, and anesthesia was maintained using the step-down infusion regimes of propofol. Propofol concentration in the plasma was measured by HPLC with a fluorescence detector. The simulation curves, following the two-compartment model, fitted well to the profiles of the individual data of propofol concentrations in the plasma. When 4 mg/kg/h of propofol was administered to both patients while maintaining anesthesia, propofol concentrations in the plasma were maintained at over 1.0 μg/ml. In patient A, the propofol concentration in the plasma was 140 ng/ml at 6 h after the end of the infusion. In patient B, the propofol concentrations in the plasma were 73 ng/ml at 6 h and 35 ng/ml at 12 h after the end of the infusion. The apparent distribution volumes of patients A and B were 1.43 and 1.62 l/kg, respectively. The half-lives of propofol in the plasma of patients A and B were estimated to be 13.3 and 17.4 min as the α phase, and 10.1 and 10.5 h as the β phase, respectively. In elderly patients with cardiac surgery, the maintenance concentrations of propofol in the plasma were enough to maintain a concentration of 1.0 μg/ml, and the half-life may be longer than previously reported values in adult patients.

Key words propofol; pharmacokinetic; total intravenous anesthesia

Intravenous infusion of propofol induces a rapid and smooth onset and clearing of anesthesia, and has minimal accumulation in the body over long-term administration.1,2 Propofol anesthesia enables the smooth maintenance of unconsciousness devoid of excitatory problems.3—4 Propofol is increasingly used for cardiac anesthesia and postoperative sedation. Since pharmacokinetic parameters vary among distinct patient populations, rational drug dosing for cardiac surgery patients is dependent on the characterization of the drug’s pharmacokinetic parameters in coronary artery bypass graft. The pharmacokinetic profile of propofol, with its short elimination half-life and high total body clearance makes it ideally suited for administration as an infusion. However, many factors (age, weight, drug interaction, and pre-existing disease) alter propofol’s pharmacokinetic properties. Of these, age is one of the most important factors. There have been reports of the pharmacokinetics of propofol infusion in Japanese patients.5 However, there have been few reports of the pharmacokinetics of propofol in elderly patients with coronary diseases under surgery. In this study, we investigated the pharmacokinetics of propofol in two elderly patients with angina pectoris undergoing coronary artery bypass graft.

Case Reports A 78-year-old Japanese man (164 cm, 64 kg, patient A) with unstable angina pectoris was operated on in an off pump coronary artery bypass graft under total intravenous anesthesia with propofol after written informed consent was obtained. The liver function was normal (GOT: 22.0, GPT: 22.7) before the operation. Propofol (Diprivan® injection) was purchased from Astra Zeneca Co., Ltd. (Osaka, Japan). For the induction of anesthesia, 1.5 mg/kg propofol (96 mg) was administered as a single bolus infusion. From 20 min after the end of the bolus infusion, anesthesia was maintained using the step-down infusion regimens of propofol with an infusion pump, at 10 mg/kg/h for 10 min, 8 mg/kg/h for 10 min, 6 mg/kg/h for 5 min, 4 mg/kg/h for 30 min, 8 mg/kg/h for 10 min, 6 mg/kg/h for 50 min, 4 mg/kg/h for 190 min, and 3 mg/kg/h for 40 min until the end of the surgical procedure (total 1792 mg of propofol). Blood samples were collected at 5 min from the end of the bolus infusion, and at 60, 120, 195, 240, 300, 365, 395, 425 and 725 min.

A 76-year-old Japanese man (162 cm, 64.1 kg, patient B) with unstable angina pectoris was operated on in a minimally invasive direct coronary artery bypass graft under total intravenous anesthesia with propofol after written informed consent was obtained. The liver function was normal (GOT: 23.5, GPT: 20.1) before the operation. For the induction of anesthesia, 1.5 mg/kg propofol (100 mg) was administered as a single bolus infusion. Anesthesia was maintained using the step-down infusion regimens of propofol using the infusion pump, at 10 mg/kg/h for 20 min, 8 mg/kg/h for 10 min, 6 mg/kg/h for 10 min, 4 mg/kg/h for 30 min, 6 mg/kg/h for 30 min, 4 mg/kg/h for 60 min, 2 mg/kg/h for 60 min, and 1 mg/kg/h for 60 min of fentanyl were administered using the infusion pump. Blood samples were collected at 5 min from the end of the bolus infusion, and at 75, 155, 210, 265, 280, 350, 640 and 1000 min.

In both patients, following the induction of anesthesia, 0.1 mg/kg vecuronium was administered as a muscle relaxant and 5 μg/kg fentanyl as a single bolus infusion. Under maintained anesthesia, 4 μg/kg for 60 min, 3 μg/kg for 60 min, 2 μg/kg for 60 min, and 1 μg/kg for 60 min of fentanyl were administered using the infusion pump.

METHODS

Measurement of Propofol Concentration Samples were cooled immediately to 4°C, and stored at that temperature for subsequent analysis. The plasma concentration of
Propofol was measured using HPLC equipped with a fluorescence detector, as described by Vree et al. Propofol was kindly supplied by Astra Zeneca (Osaka, Japan). Methanol and acetonitrile were of HPLC grade. All other chemicals were of analytical grade. Briefly, 0.1 ml of plasma was mixed with 0.5 ml methanol. Following centrifugation, 20 µl was injected for HPLC. Quantitative analysis of propofol was performed using an HPLC system (Waters Corp., MA, U.S.A.) consisting of a model 600E, a 717 plus Autosampler, a model 474 variable fluorescence detector, and a model 805 data station. A reversed-phase Puresil C-18 column (150×3.9 mm i.d.; Waters Corp., MA, U.S.A.) was used for the separation of propofol. The column was eluted with an isocratic mixture of water, acetonitrile, and methanol (v/v 4:5:1) at a flow rate of 1.0 ml/min. The eluents were monitored for fluorescence at wavelengths of 276 nm for excitation and 310 nm for emission. The lower limit for propofol detection was 20 ng/ml. Standard curves were linear between 20 ng/ml and 4 µg/ml. The within- and between-day coefficients of variation were less than 5%.

Pharmacokinetic Analysis The pharmacokinetic parameters of propofol in the plasma were estimated using a modified microcomputer program (MULTI) with a microcomputer, model NEC PC-9801, in a two-compartment model.

RESULTS

The plasma concentrations and simulation curves in a two-compartment model of propofol in patients A and B are shown in Figs. 1a and b, respectively.

The simulation curves following the two-compartment model fitted well to the profiles of the individual data of propofol concentrations in the plasma. When 4 mg/kg/h of propofol was administered to both patients while maintaining anesthesia, the propofol concentrations in the plasma were maintained at over 1.0 µg/ml. In patient A, the propofol concentration in the plasma was 140 ng/ml at 6 h after the end of the infusion. In patient B, the propofol concentrations in the plasma were 73 ng/ml at 6 h and 35 ng/ml at 12 h after the end of the infusion.

Table 1 shows the calculated values of the pharmacokinetic parameters in the two patients. The apparent distribution volumes of patients A and B were 1.43 and 1.62 l/kg, respectively. The half-lives of propofol in the plasma of patients A and B were estimated to be 13.3 and 17.4 min as the α phase and 10.1 and 10.5 h as the β phase, respectively.

DISCUSSION

The pharmacokinetic profile of propofol, with its short elimination half-life and high total body clearance, makes it ideally suited for administration as an infusion. However, many factors (age, weight, drug interaction, and pre-existing disease) alter propofol’s pharmacokinetic properties. Of these, age is one of the most important factors.

The pharmacokinetics of propofol have been described using a three-compartment linear model with compartments representing plasma, rapidly equilibrating tissues, and slowly equilibrating tissues. However, under clinical treatment, we could not obtain enough sampling points at short periods after the infusion to estimate many pharmacokinetic parameter values for the rapidly and slowly equilibrating tissue compartments of the three-compartment model. The elimination profiles of propofol after infusion in our patients followed a two-phase decay pattern. In addition, the simulation curves fitted well to the profiles of the individual data on the propofol concentration in the plasma. We judged it suitable to estimate the pharmacokinetic parameters...

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**Table 1. Calculated Values of the Pharmacokinetic Parameters in Patients**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient A</th>
<th>Patient B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>1792</td>
<td>1489</td>
</tr>
<tr>
<td>Duration of infusion (min)</td>
<td>345</td>
<td>275</td>
</tr>
<tr>
<td>𝑉d (l)</td>
<td>91.5</td>
<td>103.6</td>
</tr>
<tr>
<td>𝐾12 (h⁻¹)</td>
<td>1.114</td>
<td>0.307</td>
</tr>
<tr>
<td>𝐾32 (h⁻¹)</td>
<td>0.105</td>
<td>0.082</td>
</tr>
<tr>
<td>𝐾e (h⁻¹)</td>
<td>1.887</td>
<td>1.916</td>
</tr>
<tr>
<td>𝛼 (h⁻¹)</td>
<td>3.038</td>
<td>2.395</td>
</tr>
<tr>
<td>𝛽 (h⁻¹)</td>
<td>0.067</td>
<td>0.066</td>
</tr>
<tr>
<td>𝑇1/2,𝛼 (min)</td>
<td>13.7</td>
<td>17.4</td>
</tr>
<tr>
<td>𝑇1/2,𝛽 (h)</td>
<td>10.1</td>
<td>10.5</td>
</tr>
</tbody>
</table>

*𝑉d: apparent distribution volume, 𝐾12, 𝐾32: first-order distribution rate constants, 𝐾e: first-order elimination rate constant, 𝛼 + 𝛽 = 𝐾12 + 𝐾32 + 𝐾e, 𝛼 = 𝐾12(𝐾32 + 𝐾e) 𝑇1/2,𝛼: initial decay half-life (0.693/α), 𝑇1/2,𝛽: second decay half-life (0.693/β).*
of propofol in the plasma using a two-compartment model, taking into consideration the sampling points.

In a study of Japanese adult patients (46±16 years-old), the blood propofol concentration when the patients opened their eyes in response to a verbal command was 793.0±67 ng/ml (mean±S.D.). In our study, when 4 mg/kg/h of propofol was administered to both patients (78 and 76 years old) while maintaining anesthesia, the plasma concentrations of propofol were maintained at over 1.0 μg/ml. Schnider et al. reported that the pharmacokinetics of propofol change with age. With increasing patient age, the dose of propofol needed to achieve a defined anesthetic endpoint (dose-re-requirement) decreases. This dose does not appear to reflect an age-related change in pharmacodynamics or brain sensitivity, as measured by EEG burst suppression. Indeed, the steady state observations showed increasing sensitivity to propofol in elderly patients, with the effect-site propofol concentrations associated with 50% of the peak activation values for loss of consciousness being 2.35, 1.8, and 1.25 μg/ml in volunteers who were 25, 50, and 75 years old, respectively. Elderly patients are more sensitive to the hypnotic and EEG effects of propofol than younger people. In WISW rats, the age-dependent difference in potency of propofol showed susceptibility to certain side-effects, and these may relate to the pharmacokinetic and pharmacodynamic variance. The effects of propofol are thus recommended for the initiation and maintenance of sedation/anesthesia in elderly patients. In elderly Japanese patients, for maintaining anesthesia, plasma concentrations of propofol might be enough if maintained over 1.0 μg/ml.

Discontinuation of the recommended doses of propofol after the maintenance of anesthesia for approximately one hour result in a prompt decrease in the blood propofol concentration and rapid awakening. Longer infusions result in the accumulation of significant tissue stores of propofol, such that the reduction in the circulating propofol is slower and the time to awakening is increased. In our patients, the duration times of propofol were 345 and 275 min, respectively. When we obtained plasma samples at the longer times after the end of the infusion of propofol, for example at 6 or 12 h, plasma concentrations of propofol were detectable in both patients. Therefore, the half-lives of propofol in the plasma were estimated to be 13.7 and 17.4 min as the α phase and 10.1 and 10.5 h as the β phase, respectively. However, the liver functions of both patients were normal. We thought that there may have been an accumulation of tissue stores of propofol in our patients, even from 4 to 6 h infusion of propofol. The half-life of propofol in plasma may be longer than previously reported values in adult patients (about 3 h). Consequently there is the possibility of an accident happening after the operation, such as tumbling, falling, or tottering, because the propofol accumulated in the tissue compartment is redistributed to the plasma compartment for a long time, even after awakening from anesthesia.

REFERENCES