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Pharmacokinetic profile of propofol after a single-dose injection during general anesthesia in Japanese adults

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Abstract

Purpose. To determine the pharmacokinetic parameters of propofol after a single-dose injection in Japanese adults.

Methods. This study was carried out in adult patients who underwent minor surgery under general anesthesia with sevoflurane. We injected 1.0, 1.5, or 2.0 mg·kg^{-1} of propofol at a constant rate using a syringe pump. Arterial blood samples were taken for 480 min after the administration of propofol. The whole-blood concentration of propofol was determined with gas chromatography, and a time–blood concentration curve was analyzed by a two-compartment open-model analysis and a model-independent analysis.

Results. The half-lives of the central and peripheral compartment ($t_{1/2}\alpha$ and $t_{1/2}\beta$) were 2.26 ± 0.69 and 47.9 ± 22.1 min, respectively. The volume of the central compartment (V_c) was 0.582 ± 0.170 l·kg^{-1}, and the apparent volume of distribution at a steady state (V_{dss}) was 2.62 ± 1.061·kg^{-1}. The total body clearance (Cl) and mean residence time (MRT) were 53.7 ± 11.9 ml·min^{-1}·kg^{-1} and 98.1 ± 16.4 min, respectively.

Conclusions. Among the pharmacokinetic parameters determined in Japanese adults, $t_{1/2}\alpha$, $t_{1/2}\beta$, and Vc were similar, V_{dss} was smaller, and Cl was larger, as compared with values in Caucasians. These findings suggest that propofol could be eliminated well during minor surgery in Japanese adults.

Key words Pharmacokinetics · Propofol · Compartment analysis · Moment analysis

Introduction

Propofol is one of the most commonly used intravenous anesthetics for general anesthesia. Many studies have been carried out to determine its pharmacokinetic parameters, which make propofol particularly suitable for target controlled infusion (TCI) and total intravenous infusion (TIVA). Although TCI and TIVA are becoming increasingly popular in Japan, there is little information about the pharmacokinetic parameters of propofol in Japanese subjects [1]. In Oriental patients, it was reported that clearance was different from that in Caucasian patients; however, the subjects in these reports underwent either coronary artery surgery [2] or cesarean section [3]. We therefore determined the pharmacokinetic parameters of propofol after a single-dose injection in Japanese adults undergoing minor surgery under general anesthesia with sevoflurane.

Patients and methods

After giving informed consent, eight patients (ASA physical status 1 or 2; six men and two women) undergoing orthopedic or otological surgery under general anesthesia participated in this study. Patients who had liver or renal dysfunction or who were pregnant were excluded.

The patients were premedicated with atropine intramuscularly 30 min before arrival at the operation theater. A peripheral intravenous line was secured at the upper extremity, and acetated Ringer's solution was infused at a rate of 5–6 ml·kg^{-1}·h^{-1}. The radial artery was cannulated for blood sampling and measurement of arterial pressure. Five minutes after giving 100 μg of fentanyl, we began to inject 1.0, 1.5, or 2.0 mg·kg^{-1} of propofol at a constant rate of 20 ml·min^{-1} (200 mg·min^{-1}) using a syringe pump (Terumo, Tokyo, Japan). Vecuronium, 1 mg·kg^{-1}, was injected to facilitate endotracheal intubation. Additional thiamylal was injected when the anesthesia was considered inappropriate. Anesthesia was maintained with 4 l·min^{-1} of nitrous oxide and 1.0%–1.5% sevoflurane in 2 l·min^{-1} of oxygen.

Arterial blood samples of 1.0 ml were taken 2, 4, 6, 8, 10, 15, 30, 45, 60, 120, 180, 240, and 480 min after

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Table 1. Demographic data of the patients

Case	Age (yr)	Sex	Height (cm)	Weight (kg)	Dose ($mg \cdot kg^{-1}$)	Surgery	Duration (min)	Blood loss (g)	Urine (ml)
1	61	F	154	46	1	Cochlear implants	235	100	1500
2	48	F	157	77	1.5	Tympanoplasty	205	180	600
3	27	M	173	53	1	Tympanoplasty	170	30	850
4	22	M	176	60	1	Osteoplasty	283	50	1180
5	39	M	166	60	1	Tympanoplasty	180	10	580
6	24	M	171	53	2	Tympanoplasty	155	10	450
7	30	M	170	60	2	Tympanoplasty	140	20	620
8	35	M	166	70	2	Tympanoplasty	150	10	680
Mean	35.8	—	167	60	—	—	190	51	808
SD	13.3	—	8	10	—	—	49	60	357

Table 2. Microconstants and hybrid parameters by the analysis of two-compartment open model

Case	k_{12} (min^{-1})	k_{21} (min^{-1})	k_e (min^{-1})	A ($\mu g \cdot ml^{-1}$)	B ($\mu g \cdot ml^{-1}$)	α (min^{-1})	β (min^{-1})
1	0.111	0.0586	0.1060	1.40	0.247	0.251	0.0247
2	0.197	0.0443	0.0918	2.98	0.329	0.319	0.0123
3	0.126	0.0311	0.0607	1.05	0.131	0.209	0.0091
4	0.165	0.0535	0.0649	1.15	0.215	0.300	0.0128
5	0.170	0.0429	0.0656	1.30	0.188	0.267	0.0105
6	0.277	0.1490	0.2020	4.28	0.964	0.576	0.0522
7	0.226	0.0432	0.0092	3.76	0.389	0.350	0.0114
8	0.270	0.0912	0.1260	3.87	0.690	0.463	0.0249
Mean	0.193	0.0642	0.091	2.47	0.394	0.342	0.0197
SD	0.062	0.0386	0.057	1.39	0.288	0.122	0.0145

k_{12}, k_{21}, First elimination constant from central to peripheral compartment and from peripheral to central compartment, respectively; k_e, first elimination constant from central compartment; α, β, hybrid rate constants; A, B, constants derived from the equations [$A/\alpha + B/\beta$ = AUC] and [A + B = dose/V_c].

propofol administration. When surgery was completed prior to 480 min, the rest of the samples were obtained in the postanesthesia care unit or the general ward. The samples were refrigerated, and the blood concentration of propofol was determined with a gas chromatography (HP-G1800B GCD system, Hewlett-Packard, Palo Alto, CA, USA) [4]. The time–blood concentration curve was analyzed by a two-compartment open model using the Gauss-Newton method with the computer program MULTI [5], and the pharmacokinetic parameters were determined when AIC (Akaike's information criterion) was minimal [6]. The data are presented as means ± SD.

Results

The demographic data are presented in Table 1. All anesthesia was completed uneventfully, and no complications were noted. Blood concentration analyses were carried out up to 480 min in all patients. Computed microconstants and hybrid parameters are presented in Table 2. The values determined by the compartment and moment analyses are presented in Table 3. In brief, the half-lives of the central and peripheral compartment ($t_{1/2}\alpha$ and $t_{1/2}\beta$) were 2.26 ± 0.69 and 47.9 ± 22.1 min, respectively. The volume of the central compartment (V_c) was 0.582 ± 0.170 $l \cdot kg^{-1}$, and the apparent volume of distribution at steady state (V_{dss}) was 2.62 ± 1.061 $\cdot kg^{-1}$. The total body clearance (Cl) and mean residence time (MRT) were determined as 53.7 ± 11.9 $ml \cdot min^{-1} \cdot kg^{-1}$ and 98.1 ± 16.4 min, respectively.

Discussion

Propofol has a short duration of action and provides a smooth recovery from anesthesia. From its pharmacokinetic aspects, V_c and V_{dss} are correlated with the dose requirements, and their short half-lives indicate rapid emergence from anesthesia. These pharmacokinetic features have clinical significance following repeated

Table 3. Pharmacokinetic parameters

Case	$t_{1/2}\alpha$ (min)	$t_{1/2}\beta$ (min)	V_c (l)	V_c ($l \cdot kg^{-1}$)	V_{dss} (l)	V_{dss} ($l \cdot kg^{-1}$)	Cl ($l \cdot min^{-1}$)	Cl ($ml \cdot min^{-1} \cdot kg^{-1}$)	AUC ($\mu g \cdot min^{-1} \cdot ml^{-1}$)	MRT (min)
1	2.76	28.1	27.8	0.604	81	1.75	2.95	64.1	17.8	82.4
2	2.17	56.3	36.2	0.470	202	2.62	3.33	43.2	39.3	96.3
3	3.32	76.6	46.6	0.879	235	4.43	2.83	53.4	19.1	94.6
4	2.56	54.1	44.0	0.733	180	3.00	2.85	47.5	26.8	132.4
5	2.59	65.9	40.2	0.670	199	3.32	2.64	44.0	25.6	111.8
6	1.20	13.3	20.2	0.381	58	1.09	4.09	77.2	38.4	86.1
7	1.98	60.9	28.9	0.482	181	3.02	2.67	44.5	48.0	89.3
8	1.49	27.8	30.7	0.439	122	1.74	3.88	55.4	44.9	91.8
Mean	2.26	47.9	34.3	0.582	157	2.62	3.16	53.7	—	98.1
SD	0.69	22.1	9.00	0.170	63	1.06	0.56	11.9	—	16.4

$t_{1/2}\alpha$, Half-life of central compartment; $t_{1/2}\beta$, half-life of peripheral compartment; V_c, volume of central compartment; V_{dss}, volume of distribution at steady state; AUC, area under the time–blood concentration curve; Cl, total body clearance; MRT, mean residence time.

administration or continuous infusion of propofol [7].

Propofol is metabolized, primarily in the liver, to inactive metabolites, which are excreted in the urine. Therefore pharmacokinetic values of propofol may be affected by the metabolic condition of the subjects. However, the patients in the present study had no hepatorenal dysfunction. We then considered that the metabolic condition in these patients had less effect on the pharmacokinetic parameters of propofol.

Two different compartment models are reported for the analysis of propofol: a two- and a three-compartment model. Previous studies on the pharmacokinetics of propofol have used primarily a three-compartment open model. However, blood samples must be taken for up to 1000 min for this analysis. In this study, we were unable to take arterial blood samplings for such a long period. Therefore, we chose a two-compartment model.

Shafer et al. determined pharmacokinetic variables after continuous infusion by using a two-compartment model, and reported that $t_{1/2}\alpha$ and $t_{1/2}\beta$ were 4.6 ± 1.6 and 116 ± 34 min, with V_{dss} of 159 ± 57 l and Cl of 2.09 ± 0.65 $l \cdot min^{-1}$ [8]. These were equal to or greater than the values we found, suggesting a difference in race. In Caucasians, investigated after a single-bolus injection with a three-compartment open model, $t_{1/2}\alpha$ and $t_{1/2}\beta$ ranged from 1.8 to 4.1 min and from 30 to 69 min, respectively [9–11]. V_c, Cl, and V_{dss} ranged from 19.6 to 41.3 l, 1.44 to 1.91 l·min, and 171 to 771 l, respectively, in their report, whereas we found similar values of $t_{1/2}\alpha$, $t_{1/2}\beta$, and V_c, somewhat smaller values of V_{dss}, and larger values of Cl. In young Japanese volunteers analyzed with a three-compartment open model [1], $t_{1/2}\alpha$ and $t_{1/2}\beta$ were 2.6 ± 1.2 and 51.0 ± 11.7 min, respectively, which were similar to our values, but V_{dss} and Cl were 317 ± 132 l and 1.62 ± 0.41 $l \cdot min^{-1}$, respectively, which were different from ours. These differences can be partly explained by the difference in compartment models and in the range of patient ages. In a model-independent analysis in Chinese women receiving a bolus dose of 2 $mg \cdot kg^{-1}$ of propofol, V_{dss} was 3.36 ± 1.87 $l \cdot kg^{-1}$ and Cl was 29.40 ± 8.72 $ml \cdot min^{-1} \cdot kg^{-1}$ [3]. However, this report is not compatible with ours, since the clinical settings were different in type of surgery and bleeding.

It is considered that inhalational anesthetics affect the pharmacokinetic properties of propofol. Halothane provides a drug–drug interaction to interfere with the pharmacokinetics of propofol and alters the amount of propofol needed to achieve or supplement a given depth of anesthesia [12]. Although the influence of sevoflurane on the pharmacokinetic profile of propofol has not been well clarified, the difference in depth of anesthesia among patients may partially account for interindividual variability in pharmacokinetic values.

To determine the concentration of propofol in whole blood, both liquid and gas chromatography are currently available. We used gas chromatography in this study because this method has considerable advantages in rapidity, simplicity, and accuracy. Our coefficient of variation was 2.14%, which was superior to other results with high-performance liquid chromatography [4].

Theoretically, blood loss might affect the pharmacokinetic properties of agents injected into the circulation. However, blood loss was minimal in the present study. It is also considered that increased urination accelerates excretion of the circulating agents. Because propofol is known to be metabolized in the liver and can be used even in a patient with renal failure without prolongation of its half-life [13], we do not believe that variation in urine volume affected our analysis of the variables.

TCI and TIVA are currently becoming popular in Japan. However, available infusion regimens are based on pharmacokinetic data reported from other countries. Since there is little information about the pharmacokinetic profile of propofol in Japanese patients, our

results may contribute to a computational basis for such purposes.

In summary, in our patients $t_{1/2}\alpha$, $t_{1/2}\beta$, and Vc, were similar to those of Caucasians, V_{dss} was smaller than in Caucasians, and Cl was larger than in Caucasians. These results suggest that propofol could be eliminated well during minor surgery in Japanese adults.

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