

Pharmacokinetics of Long-Term Propofol Infusion Used for Sedation in ICU Patients

Jacques Albanese, M.D.,* Claude Martin, M.D.,† Bruno Lacarelle, Ph.D.,‡
Pierre Saux, M.D.,§ Alain Durand, Ph.D.,‡ François Guoin, M.D.†

The pharmacokinetics of propofol were determined in nine patients (seven men, two women, (mean \pm SD) 55.8 \pm 21.2 yr, 65.2 \pm 8 kg) requiring prolonged mechanical ventilation of their lungs. After an initial dose of 1-3 mg/kg, propofol was administered iv at 3 mg/kg/h for 72 h. Arterial blood samples were collected at selected times during and up to 72 h after infusion. Propofol whole blood concentrations were determined by high-performance liquid chromatography with fluorescence detection. Individual pharmacokinetic parameters were estimated by noncompartmental analysis. Derived pharmacokinetic parameters showed a long terminal phase ($T_{1/2} = 1878 \pm 672$ min), a large volume of distribution at steady state ($V_{d,ss} = 1666 \pm 756$ l), and a high total body clearance ($Cl = 1.57 \pm 0.56$ l/min). While the propofol terminal elimination half-life is longer than that previously reported, emergence from sedation after prolonged administration will be governed by both redistribution mechanisms arising from the large distribution volumes and elimination from the body. (Key words: Pharmacokinetics: long-term infusion. Anesthetics, intravenous: propofol.)

PATIENTS IN Intensive Care Units (ICU) undergoing prolonged mechanical ventilation of their lungs may require sedation. Ideally, the sedative drug used should be rapidly eliminated to prevent prolonged clinical effects once it is discontinued. Rapid reversibility of the sedation is needed to assess the patient's neurologic status and to avoid unnecessary prolongation of mechanical ventilation. Some reports on propofol pharmacokinetics after bolus injections¹⁻³ or brief infusions,⁴ suggest that this drug has these attributes because of a high total body clearance and a relatively short elimination half-life. However, some other reports suggest that propofol may accumulate² which, during long-term infusion, could lead to undesirable prolongation in its terminal elimination half-life. To date limited pharmacokinetic information is available on the use of propofol for prolonged sedation in ICU pa-

tients. Therefore we studied the pharmacokinetics of propofol administered by continuous infusion to a group of patients requiring prolonged controlled mechanical ventilation of their lungs.

Methods

After institutional and families' approvals were obtained, nine consecutive patients were included in the study. They were free from cardiovascular, renal, and hepatic abnormalities. They all required prolonged controlled mechanical ventilation of their lungs for neurologic diseases or acute respiratory failure (table 1). Respiratory rate, tidal volume, and FI_{O_2} were adjusted to obtain normocapnia (Pa_{CO_2} : 39 \pm 2 mmHg) and a Pa_{O_2} greater than 80 mmHg.

Patients were first given a bolus induction dose of 1-3 mg/kg propofol (commercial emulsion formulation, Diprivan® ICI), after which the drug was administered by continuous infusion at a constant flow-rate of 3 mg \cdot kg⁻¹ \cdot h⁻¹ for 72 h through a central venous catheter. Arterial blood samples were obtained for blank assay before propofol injection at 1, 20, 40 min, and at 1, 2, 4, 6, 18, 30, 48, 54, 66, 72 h after the beginning of infusion. Further samples were taken at 5, 10, 20, 40 min, and 1, 2, 6, 12, 24, 36, 48, 60, 72 h after the end of infusion. Each 5-ml sample was collected in tubes containing potassium oxalate. The tubes were shaken and stored at 4°C until assayed. Propofol whole blood concentrations were determined using a slight modification of the high-performance liquid chromatography (HPLC) method described by Plummer *et al.*⁵ To a whole blood sample (1 ml) internal standard (Thymol, Millipore, Milford, MA), sodium dihydrogen orthophosphate 0.1 M (1 ml) and cyclohexane (5 ml) were added. The organic phase was then alkalinized with 10 μ l of alcoholic KOH (0.1 M) and then evaporated to dryness under nitrogen. After reconstitution with mobile phase (100 μ l), the residual was analyzed by HPLC with fluorescence detection (Shoefel GM 970). The excitation and emission wavelengths were 276 nm and 310 nm, respectively. A C₁₈ μ Bondapack column (Waters Assoc., ICI Pharmaceuticals, Maccles Field, UK) equipped with a guard-pack column (Waters Assoc.) was used. The mobile phase consisted of acetonitrile/water/orthophosphoric acid (85%), 60/40/02, and was delivered at a flow rate of 1.5 ml/min with a model M 45 HPLC pump (Waters Assoc.). Two calibration ranges

* Assistant in Anesthesiology, Hôpital Nord, Marseille, France.

† Professor of Anesthesiology, Hôpital Sainte Marguerite, Marseille, France.

‡ Assistant in Pharmacology, Hôpital la Timone, Marseille, France.

§ Assistant in Anesthesiology, Hôpital Sainte Marguerite, Marseille, France.

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Address reprint requests to Dr. Albanese: Departement d'Anesthesie, Hôpital Nord, Chemin des Bourrely, 13326 Marseille Cedex 15, France.

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TABLE 1. Diagnosis and Reasons for Mechanical Ventilation at Time of Admission to the ICU

Patient	Diagnosis	Age (yr)	Weight (kg)
1	Meningitis	30	72
2	Acute respiratory failure	75	50
3	Postischemic brain damage	25	55
4	Head trauma	27	75
5	Postischemic brain damage	77	65
6	Acute respiratory failure	72	65
7	Acute respiratory failure	55	70
8	Acute respiratory failure	65	65
9	Head trauma	77	70
Mean ± SD		55.8 ± 21.2	65.2 ± 7.6

were used: 25–100 ng/ml (internal standard: 25 ng/ml) and 100–1,000 ng/ml (internal standard: 200 ng/ml). For propofol concentrations higher than 1,000 ng/ml, samples were diluted with whole blood. The coefficient of variation of the assay was 9.2% for a concentration of 750 ng/ml and 10% for concentration of 100 ng/ml.

Individual pharmacokinetic parameters were estimated by noncompartmental analysis for all patients. This method was chosen because of an irregular elimination profile in which significant increase in blood concentrations was observed in most patients after the end of infusion. The terminal half-life ($T_{1/2}$) was obtained using a linear regression on the natural log of the postinfusion decay. Area under the time-blood concentration curve (AUC) to infinite time and area under the moment curve

(AUMC) to infinite time were computed as described by Benet and Galeazzi.⁶ Clearance was derived from the area under the concentration curve *versus* time from zero to infinity. Mean residence time (MRT) was calculated from AUMC and AUC ($MRT = AUMC/AUC - T/2$, where T is time for infusion stop), and volume of distribution at steady state from MRT and clearance ($Vd_{ss} = MRT \times \text{clearance}$).⁷

Results

Propofol blood concentrations *versus* time are shown in figure 1. After an initial peak (range: 775–15,305 ng/ml) from the loading dose, there was a decrease in blood concentration (1300 ± 500 ng/ml at the sixth hour) which in turn was followed by a gradual increase. A plateau was nearly reached at hour 30 and maintained up to hour 72 when the infusion was stopped. Between the first and the second hour after the end of infusion, a significant increase in blood concentration was observed. Then propofol blood concentrations decreased with a curvilinear profile during the period of sampling (up to 72 h) after the end of infusion.

Table 2 presents the pharmacokinetic parameters for all patients.

Discussion

The aim of this study was to establish the pharmacokinetic profile of propofol given by prolonged continuous

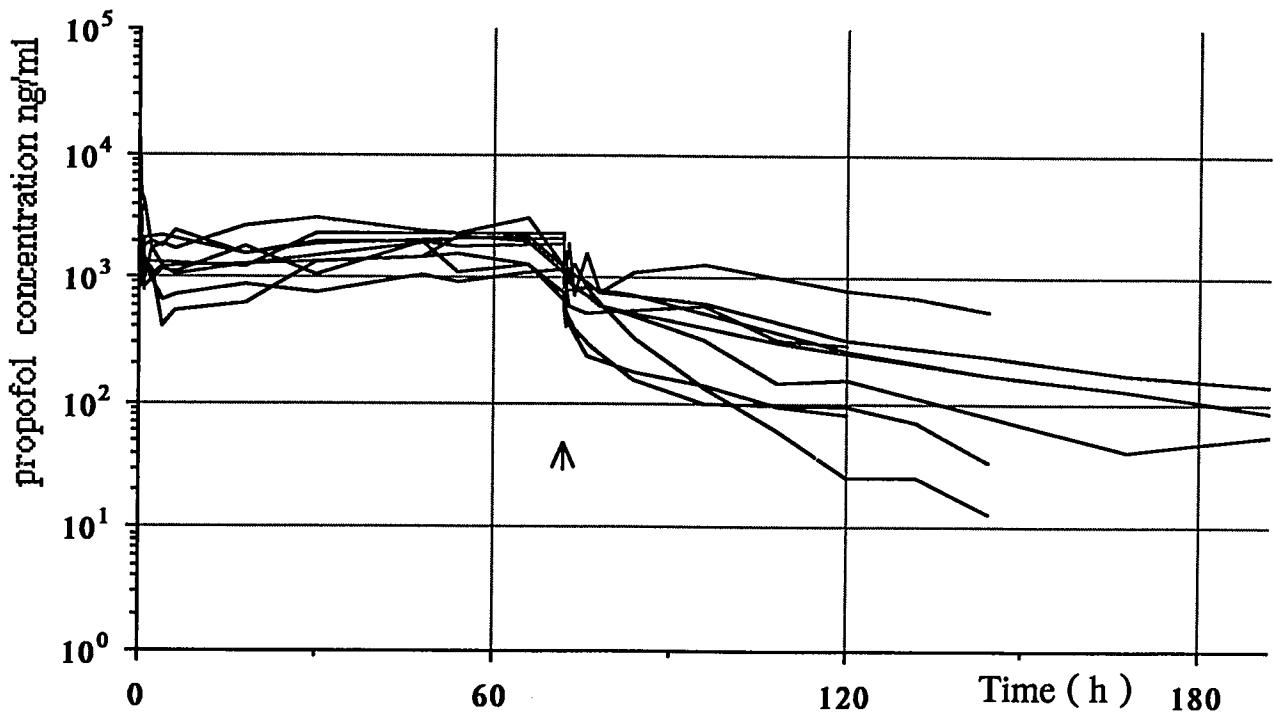


FIG. 1. Individual blood propofol concentrations for the nine patients. Infusion was discontinued at 72 h (arrow).

TABLE 2. Propofol Pharmacokinetic Parameters Derived from Noncompartmental Data Analysis in the Nine Patients

Patient	1	2	3	4	5	6	7	8	9	Mean \pm SD
$T_{1/2}$ (min)	1674	3000	726	1734	1206	2736	2088	2166	1578	1878 \pm 672
$V_{d_{ss}}$ (l)	1288	2836	415	1199	777	2264	1834	2439	1943	1666 \pm 756
CL (l/min)	2.58	1.1	1.53	2.56	1.48	1.21	1.48	0.95	1.25	1.57 \pm 0.56

infusion in patients requiring sedation for mechanical ventilation. After an initial bolus dose of 1–3 mg/kg, depending on hemodynamic status, propofol was infused at rate of $3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. This infusion rate has been demonstrated to provide a propofol concentration at steady state (C_{ss}) of approximately 2,000 ng/ml and sleep in more than 90% of patients.^{4,8} It has also been shown that the response to surgical stimulation in nonmajor surgery was suppressed when propofol blood concentrations were between 2,000 and 3,000 ng/ml.⁸ We speculated that a blood propofol concentration of 2,000 ng/ml was sufficient for a clinical sedation in patients not subjected to surgical stimulus. Indeed, this propofol C_{ss} was achieved in most of our patients.

The pharmacokinetic data of our patients are different from those reported in studies using short-term infusions,⁵ or repeated iv bolus⁹ or single iv injection.^{2,8–11} The main findings of this study is that during prolonged infusion, the $T_{1/2}$ of propofol was found to be prolonged and the steady-state distribution volume increased so that total body clearance was similar to that reported in other studies.^{2,4,5,9} This could be explained by the fact that we performed blood sampling during a prolonged period of time (72 h after cessation of infusions). This has already been shown by Campbell *et al.*¹² who demonstrated in their study that propofol termination half-life correlated strongly with the length of the sampling period. The patient in whom the sampling period exceeded 42 h had termination half-life greatly exceeding prior estimates based on shorter sampling periods. They concluded that sampling periods longer than 8–12 h should be considered for accurate and reliable determination of propofol kinetics. However, even in the present study our sampling period was only about twice the $T_{1/2}$ instead of the recommended three or more times. The very high values of $V_{d_{ss}}$ indicate that propofol is extensively distributed from the blood into tissues.^{4,10} This suggests that after injection, propofol was rapidly cleared from the blood during distribution, but a significant proportion remained in the tissues (the deep compartment, presumably lipid).

The secondary peaks seen in propofol blood concentrations soon after cessation of infusion were probably related to modification in the distribution of the drug. Similar secondary peaks have been observed upon awakening with other lipophilic iv anesthetic agents such as thiopental, fentanyl, and Althesin.^{13,14} Secondary peaks

have also been reported with propofol itself.^{10,11,15} Alterations in cardiac output and regional blood flow that occur upon awakening may lead to changes in the distribution of drugs from lipid tissue.¹⁶ Our sampling method (arterial blood) does not support the hypothesis that propofol was derived from local tissues adjacent to the sampling sites.

For greater convenience, propofol was administered by constant-rate infusion. To obtain sedation, therapeutic blood concentrations of the drug, compatible with clinical sedation, will depend on the type and intensity of stimulus. Because most of the patients included in this study had neurologic disturbances (head trauma or posts ischemic brain damage), no attempt was made to correlate clinical reaction and propofol blood concentration. Nevertheless some patients exhibited signs of clinical response during bronchial suctioning or sponge bathing performed by nurses. It should be noted that a C_{ss} of 2,000 ng/ml was only achieved after 30 h, and this, associated with the interpatient variability of propofol blood concentrations, may explain why a proper level of sedation was not achieved during the first hours of sedation. To obtain a higher C_{ss} (2,500 ng/ml) more rapidly, a higher propofol infusion rate should be considered. During anesthesia procedures, Gepts *et al.*⁴ reported a C_{ss} greater than 2,500 ng/ml in 85% of patients after only 2 h using a propofol infusion rate of $6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. As to clinical implications, one should be careful with propofol infusions because the long $T_{1/2}$ may indicate a potential risk of accumulation in some patients. Clinical experience with propofol long-term infusion is still limited. In one study, Beller *et al.*¹⁵ found that infusion of propofol for 96 h allowed rapid recovery in their patients with no clinical sign of drug accumulation. Propofol blood concentrations declined in an identical manner when the constant propofol infusion was transiently terminated at 24, 48, and 72 h. These data suggest that both redistribution and high propofol clearance are important mechanisms to cause rapid decrease of blood concentrations after prolonged infusions. Further studies should be carried out to determine the exact clinical relevance of the long propofol elimination half-life demonstrated in the present study.

In conclusion, following the use of propofol by constant long-term infusion, a prolonged elimination half-life is reported. Total body clearance of the drug was high, as previously reported. The clinical relevance of this study

in term of a delayed awakening after cessation of propofol infusion has yet to be determined, because considerable interpatient variations was observed.

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