Pulmonary Disposition of Propofol in Surgical Patients

Yan-Ling He, Ph.D.,* Hiroshi Ueyama, M.D.,† Chikara Tashiro, M.D.,‡ Takashi Mashimo, M.D.,§ Ikuto Yoshiya, M.D.‖

Background: The lungs have been mentioned as a possible site contributing to the extrapulmonary clearance of propofol. The objective of the present study was to clarify the pulmonary disposition of propofol directly in human lungs by investigating both the first-pass uptake and pulmonary extraction at pseudo–steady state.

Methods: Nine patients were enrolled in the first-pass uptake study. Propofol (5 mg) and indocyanine green (ICG; 15 mg) were simultaneously administered via a central venous catheter within 1 s, and sequential arterial blood samples were obtained from the radial artery at 1-s intervals up to 45 s. Eleven patients were included in the infusion study, and propofol was infused via the jugular vein at a rate of 50 µg kg⁻¹ min⁻¹. Blood samples were simultaneously collected from pulmonary and radial arteries up to 60 min.

Results: A pronounced difference in the dilution curves between propofol and ICG was observed, and 28.4 ± 11.6% (mean ± SD) of propofol was taken up during the single passage through the human lung. The mean pulmonary transit time of propofol (31.3 ± 6.0 s) was significantly longer than that of ICG (22.4 ± 2.7 s; P < 0.01), indicating that some of the propofol trapped by lungs returned to the circulation by back diffusion. In the constant infusion study, no significant differences were observed with the plasma concentrations of propofol between pulmonary and radial arteries except for that at 2 min. The area under the curve of pulmonary and radial arterial concentration curves to 60 min were 59.1 ± 14.8 and 56.8 ± 12.5 µg ml⁻¹ min⁻¹, respectively. No significant difference was observed with the area under the curve, suggesting that metabolism was not involved in the pulmonary uptake in human lungs.

Conclusions: Most of the propofol that undergoes pulmonary uptake during the first pass was released back to the circulation by back diffusion. Metabolism was not involved in the pulmonary uptake in human lungs. (Key words: Extrapulmonary metabolism; pharmacokinetics.)

EXTRAHEPATIC clearance of propofol has been suggested because systemic propofol clearance exceeds hepatic blood flow.¹⁻⁵ Furthermore, extrapulmonary metabolism of propofol has been confirmed in patients during the anhepatic phases of liver transplantation.⁶⁻⁷ The lungs have been mentioned as a possible site contributing to the extrahepatic clearance of propofol, although there is no direct evidence for this speculation. Because the entire dose traverses the lungs, even a small fractional uptake may impact significantly on the availability and result in a lower plasma concentration. The time to peak plasma concentration and the time to peak pharmacologic effects and onset can especially be delayed when a significant amount of uptaken drugs is released back to the circulation. The first-pass pulmonary uptake for several drugs used during anesthesia in human lungs have been studied, and extensive pulmonary uptake for fentanyl and sufentanil has been demonstrated.⁸⁻¹² Although extensive first-pass uptake of propofol in cat and sheep lungs and an extensive pulmonary sequestration of propofol in rats have been reported,¹³⁻¹⁶ the pulmonary uptake of propofol in humans remains unknown. The most important clinical implication of such uptake is the effect on the initial pharmacokinetics that determines the induction dose of intravenous anesthetic drugs. The objective of the present study was to examine the pulmonary disposition of propofol directly in human lungs by investigating both the first-pass uptake and pulmonary extraction at pseudo–steady state.

Materials and Methods

Patients

This study was approved by the Institutional Review Board of Osaka University Medical School, and written informed consent was obtained from all patients enrolled in the study. The characteristics of patients are shown in table 1.

First-pass Uptake of Propofol in Patients

Nine patients scheduled for elective surgery with general anesthesia were enrolled in the study. After the induction of general anesthesia with intravenous administration of thiopental (250 mg) and vecuronium (8 mg), central venous and radial artery catheters were inserted. General anesthesia was maintained with sevoflurane (0.5–1.0%). A finger probe, which is connected to the integrated pulse-spectrophotometry monitoring system, was fixed on the tip of the finger to detect the blood concentrations of indocyanine green (ICG) based on pulse spectrophotometry.¹⁷⁻¹⁹ Before propofol administration, 0.5 ml of blood was drawn into a heparinized syringe to measure the hemoglobin concentration that is necessary for calculating the ICG blood concentration.
After baseline measurement, propofol (5 mg; Diprivan, Zeneca Pharmaceuticals, Osaka, Japan) and ICG (15 mg; Diagnogreen, Daiichi Pharmaceutical Company, Tokyo, Japan) were simultaneously administered via the central venous catheter within 1 s. Sequential arterial blood samples were collected from the radial artery at 1-s intervals up to 45 s and at 5-s intervals up to 1 min by directing the spontaneous outflow of the arterial catheter into heparinized tubes. Blood samples were immediately centrifuged at 15,000 rpm for 5 min at 4°C, and the plasma samples were stored at 4°C until subsequent analysis within 48 h.

**Data Analysis**

The cardiac output was estimated from the area under the first dilution curves (AUC) of ICG:

\[
CO = \frac{Dose}{AUC_{\text{first-pass}}} \quad (1)
\]

The concentration data of propofol and ICG were transformed to the unit mass flow, termed frequency output:

\[
f(t) = \frac{C(t) \cdot Q}{Dose} \quad (2)
\]

where \(C(t)\) is the concentration of either propofol or ICG at time \(t\), \(Q\) is equal to the cardiac output, and \(f(t)\) is the unit response of the system in terms of the fraction of injected dose per unit time. Plotted in such a manner, the AUC from time zero to the end of the first pass is equal to the availability of an injected dose through the lungs on the first passage (\(F_{\text{pul}}\)):

\[
F_{\text{pul}} = \int_0^r f(t) \, dt \quad (3)
\]

where \(t\) is the end of the first pass determined by the last point of the linear portion on a semilogarithmic plot of the descending part of the ICG dilution curve.

The pulmonary extraction ratio (\(E_{\text{pul}}\)) was calculated from \(F_{\text{pul}}\) as follows:

\[
E_{\text{pul}} = 1 - F_{\text{pul}} \quad (4)
\]

The mean pulmonary transit time (\(MTT_{\text{pul}}\)) was calculated by:

\[
MTT_{\text{pul}} = \int_0^r \frac{C(t) \cdot t \, dt}{\int_0^r C(t) \, dt} \quad (5)
\]

The apparent distribution volume (\(V_{\text{app}}\)) between the injection site and the sampling site can be estimated from:

\[
V_{\text{app}} = MTT_{\text{pul}} \times \text{cardiac output} \quad (6)
\]

For ICG, \(V_{\text{app}}\) is the intravascular volume between the site of injection (the central venous catheter) and the site of sampling (the tip of a forefinger). The difference between the \(V_{\text{app}}\) of propofol and ICG is the pulmonary tissue volume of propofol.

For comparative purposes, the conventional instantaneous extraction ratio at each time point was calculated by the following formula:

\[
E(t) = 1 - \left[ \frac{F_{\text{propofol}}(t)}{F_{\text{ICG}}(t)} \right] \quad (7)
\]

where \(F(t)\) represents the fractions of injected dose of each drug per milliliter at time \(t\), respectively.

**Measurement of Pulmonary and Radial Arterial Concentrations during a Constant Infusion**

Eleven patients undergoing coronary artery bypass graft surgery were included in this study. After the induction of anesthesia with fentanyl (0.2–0.4 mg), midazolam (5–10 mg) and vecuronium (8 mg), jugular venous, radial arterial, and pulmonary arterial catheters were inserted. Anesthesia was maintained with sevoflurane (1–2%) in oxygen. Propofol was administered via an intravenous cannula placed in the right internal jugular vein by an infusion pump (Graseby 3500, Graseby Medical Limited Inc., Hartford, United Kingdom) at a rate of 50 \(mg\) \(\frac{kg}{min}\). Blood samples were simultaneously collected from pulmonary and radial arteries at 0, 2, 3.5, 5, 7, 10, 12, 15, and 20 min and at 10-min intervals up to 60 min. Blood samples were immediately centrifuged, and the plasma samples were stored at 4°C pending assay. The AUCs for propofol plasma concentration in pulmonary and radial arteries were calculated based on the trapezoidal rule.

**Sample Analysis**

Several groups have reported that no difference was detected between whole blood and plasma concentrations of propofol; thus, the plasma concentration of propofol was measured in the present study. Plasma propofol concentration was measured using modified
high-performance liquid chromatography method reported previously with fluorescence detection. The high-performance liquid chromatography (LC-10AD; Shimadzu, Kyoto, Japan) is composed of a variable wavelength ultraviolet detector (SPD-10AD, Shimadzu) and fluorimetric detector (RF-10AD, Shimadzu), degasser (DGU-14A, Shimadzu), autoinjector (SIL-10AD, Shimadzu), and column oven (CTO-10AS, Shimadzu). Briefly, a Symmetry C18 column (3.5 mm, 4.6 × 100 mm; Waters, Osaka, Japan) was equilibrated at 1.5 ml/min with the mobile phase containing acetonitrile and water (60:40, vol). The excitation and emission wavelengths for flurometric detection of propofol were set at 276 and 310 nm, respectively. The limit of sensitivity of the assay was 0.05 μg/ml in plasma. The intraday and interday coefficients of variation at the concentration of 1.0 μg/ml were < 5%.

Blood ICG concentration was monitored noninvasively with pulse spectrophotometry. The integrated pulse-spectrophotometry monitoring system is composed of a finger probe, a monitoring device, and a computer for recording and printing the results (DDG1001, Nihon Kohden Inc., Tokyo, Japan). The blood ICG concentration was measured at every pulse interval, which was less than 1 s, according to the patient’s heart rate. At the end of each study, hemoglobin concentration was entered into the computer, and the final ICG blood concentration–time course was printed out automatically. The data files of ICG blood concentration–time course were downloaded for further data analysis. The blood concentrations of hemoglobin were measured with a radiometer (ABL 620, Radiometer, Copenhagen, Denmark) immediately after sampling.

Statistical Analysis
Data are expressed as mean values ± SD. Differences in parameters between ICG and propofol were analyzed with a paired t test. Differences in propofol concentrations between pulmonary and radial arteries at each time point were analyzed with the one-way repeated-measures analysis of variance. If the analysis of variance was found to be significant, Bonferroni correction was performed to compare the difference in propofol concentrations between pulmonary and radial arteries. A P value < 0.05 was considered statistically significant.

Results
Figure 1 shows the representative frequency outflow curves of propofol and ICG during the first pass through the lungs. Plotted in such a manner, the AUC from time zero to the end of the first pass is equal to the availability of an injected dose. A pronounced difference between the shape of the dilution curve of propofol and that of ICG was observed. ICG showed a typical shape of intravascular space with a sharp peak, whereas that of propofol showed a much lower peak and displayed slowly tailing, suggesting a reversible distribution of propofol into the lungs. The cardiac output estimated based on the ICG dilution curve was 4.91 ± 1.50 l/min for the patients participating in the first-pass study. The pulmonary uptake of propofol during the first pass through the human lung was estimated to be 28.4 ± 11.6% based on equation 4. The mean pulmonary transit time of propofol (31.3 ± 6.0 s) was significantly longer than that of ICG (22.4 ± 2.7 s; P < 0.01), indicating that some of the propofol trapped by lungs during the first pass returned to the circulation by back diffusion. The apparent distribution volume for propofol estimated based on equation 6 was 2.52 ± 0.79 l, which showed a significant larger value than that of ICG (1.67 ± 0.37 l; P < 0.001). The pulmonary tissue volume of propofol estimated from the difference between the apparent distribution volume for propofol and that for ICG was 0.866 ± 0.448 l, demonstrating an extensive distribution of propofol into the lung tissue. The instantaneous extraction ratios of propofol at each sampling time were calculated based on equation 7. The initial extraction of propofol was as high as 99% and then decreased to 18% at the end of first pass through the lungs.

Figure 2 illustrates the plasma concentrations of propofol in pulmonary and radial arteries during a constant infusion at 50 μg · kg⁻¹ · min⁻¹. The plasma concentrations of propofol in both pulmonary and radial arteries increased progressively and reached pseudo-steady state at 20 min. Peak plasma concentrations were observed at 60 min (1.14 ± 0.27 mg/ml and 1.16 ± 0.28 mg/ml). No significant differences were observed with the plasma concentrations of propofol between pulmonary and radial arteries except for that at 2 min. The significant higher plasma concentration of propofol in pulmonary artery than that in radial artery at 2 min (0.37 ± 0.26 μg/ml vs. 0.29 ± 0.23 μg/ml; P < 0.05) might be attributed to the pulmonary uptake of propofol at the initial phase or lag time between the two
Discussion

The first-pass pulmonary uptake of fentanyl, meperidine, morphine, diazepam, and thiopental have been studied in humans. These studies suggest that the extent of pulmonary uptake of drugs is related to physicochemical properties such as a basic amine moiety and lipid solubility and to physiological factors such as plasma protein binding and cardiac output. The first-pass uptake of a drug through the lungs has been calculated at the time when 95% of the injected ICG has passed through the lungs in the anesthetic field. In the present study, the first pass uptake of propofol and ICG were separately calculated based on their frequency output curves. The concept of "frequency output" was proposed to interpret the dilution curves in rat liver by Roberts and Rowland in 1986. The advantage of this expression is that the distribution properties of an indicator can be envisaged directly from the shape of the normalized frequency output curves. In addition, the availability of a drug through an organ can be directly estimated from the integral of the frequency output dilution curve in an isolated perfused organ preparation where the perfusion flow is under control.

In this study, the first-pass uptake of propofol through human lungs was estimated to be 28.4 ± 11.6%. The pulmonary extraction of propofol during the first pass through human lungs (28.4 ± 11.6%) was higher than that of thiopental (13.8 ± 1.8%), similar to that of diazepam (30.4 ± 3.7%), and lower than that of fentanyl (75.2 ± 3.2%) and meperidine (64.5 ± 7.8%). The pulmonary uptake of diazepam has been shown to be dependent on the albumin concentrations in perfusate in rat lung, where the binding of diazepam to plasma albumin limited its availability for pulmonary uptake. Roerig et al. suggested that such a mechanism may also be possible for neutral and anionic lipophilic drugs such as thiopental, i.e., binding to plasma albumin limits their partitioning into pulmonary tissue. Propofol is a weakly acidic compound that is extensively bound to the plasma proteins (97–99%). Drugs of this type are generally believed to bind to albumin in plasma. Irrespective of the high lipophilicity of propofol, the binding to plasma protein may limit its availability for uptake into lung tissue.

Kuipers et al. recently demonstrated that 30% of the propofol was eliminated during the first pass through the lungs in awake sheep, although they acknowledged that pulmonary clearance or distribution into a deep-tissue compartment could not be discerned. It is worth noting that the first-pass pulmonary uptake of propofol in awake sheep is similar to that in human lungs (28.4%) reported in the present study. On the other hand, a substantial removal of propofol by the cat lung was demonstrated (61%), which was significantly decreased to 39% and 32% in cats exposed to 1.5% halothane and pretreated with fentanyl (1 mg/kg) 30 s before propofol administration, respectively. In our human study, sevoflurane (0.5–1.0%) used for maintaining the anesthesia might have some effects on the pulmonary uptake of propofol. However, considering that 1.0% halothane (1.33 minimum alveolar concentration) did not influence the pulmonary uptake of propofol in cats (60%), a significant effect by 0.49 minimum alveolar concentration sevoflurane (1%) on the pulmonary uptake of propofol does not seem to be plausible. A species difference would also have to be kept in mind because the enzyme involved in the glucuronidation of propofol is uridine diposphosphate-glucuronosyltransferase, and a notable species difference in this enzyme was indicated.

In this study, we demonstrated that propofol was significantly taken up during the first pass through the human lung. A significant first-pass uptake in the lungs can be a result of either metabolism or distribution into lung tissue. Although extensive pulmonary uptake of propofol in cats, rats, and sheep has been reported, none of these studies can discriminate between pulmonary elimination and distribution into lung tissue. In addition to the first-pass study, we measured both the radial and pulmonary arterial propofol concentrations during constant-rate infusion. In contrast to the first-pass study, pulmonary extraction at steady state should be...
flect the metabolism rather than distribution. By combining the results from the first-pass study and that from the constant-infusion study, we were capable of distinguishing between pulmonary metabolism and pulmonary tissue distribution for the first time. In the first-pass study, the significantly longer pulmonary mean transit time of propofol than that of ICG and the decreasing instantaneous extraction ratio indicate the back diffusion of the extracted propofol during the first pass out of the lungs into blood. In the infusion study, no significant differences between the propofol concentrations in pulmonary and radial arteries were observed after 2 min, suggesting that the distribution process of propofol into lung tissue reached equilibrium within a short time of infusion. Pulmonary extraction at the steady state is likely to result from metabolism rather than distribution. The AUC to 60 min under the pulmonary arterial plasma concentration of propofol was not significantly different from that under the arterial plasma concentration curve, suggesting that the initial uptake of propofol into human lungs involves temporary sequestration, after which the propofol is released back into the circulation, probably unmetabolized.

Therefore, we conclude that it is the pulmonary distribution of propofol that resulted in a significant amount of pulmonary uptake by the human lungs during the first pass, and the lungs do not appear to contribute to the extrahepatic metabolism of propofol in the human. This is consistent with and supported by an investigation by Guellec et al., who demonstrated a lack of significant metabolism of propofol in human lung tissue. They also investigated the glucuronidation of propofol in micromolar fractions from various tissues and species, including humans, and found no activity in human lung microsomes. They concluded that kidney rather than lung might play an important role in the extrahepatic metabolism of propofol in humans. Consistent with their speculation, an efficient ability of human kidney microsomes to form propofol glucuronide has been reported. Therefore, it is reasonable to speculate that the significant pulmonary uptake of propofol during the first pass is the result of pulmonary distribution rather than metabolism.

In summary, a significant amount of propofol was taken up during the first pass through the human lung. Most of the propofol that undergoes pulmonary uptake on the first pass was released back into the circulation by back diffusion when the blood concentrations decreased. No pulmonary extraction of propofol was observed at the pseudo–steady state, suggesting that metabolism was not involved in the pulmonary uptake in human lungs. Therefore, the lungs do not seem to be a site contributing to the extrahepatic metabolism of propofol in humans.