

# Human Kidneys Play an Important Role in the Elimination of Propofol

Daisuke Takizawa, M.D.,\* Haruhiko Hiraoka, M.D., Ph.D.,† Fumio Goto, M.D., Ph.D.,‡ Koujiro Yamamoto, Ph.D.,§ Ryuya Horiuchi, Ph.D.||

**Background:** Extrahepatic clearance of propofol has been suggested because its total body clearance exceeds hepatic blood flow. However, it remains uncertain which organs are involved in the extrahepatic clearance of propofol. *In vitro* studies suggest that the kidneys contribute to the clearance of this drug. The purpose of this study was to confirm whether human kidneys participate in propofol disposition *in vivo*.

**Methods:** Ten patients scheduled to undergo nephrectomy were enrolled in this study. Renal blood flow was measured using *para*-aminohippurate. Anesthesia was induced with vecuronium (0.1 mg/kg) and propofol (2 mg/kg) and then maintained with nitrous oxide (60%), sevoflurane (1~2%) in oxygen, and an infusion of propofol (2 mg · kg<sup>-1</sup> · h<sup>-1</sup>). Radial arterial blood for propofol and *para*-aminohippurate analysis was collected from a cannula inserted in the radial artery. The renal venous sample and the radial arterial sample were obtained at the same time after the steady state of propofol was established.

**Results:** The renal extraction ratio of propofol was 0.58 ± 0.15 (mean ± SD). The renal clearance of propofol was 0.41 ± 0.15 l/min (mean ± SD), or 27 ± 9.9% (mean ± SD) of total body clearance.

**Conclusion:** Human kidneys play an important role in the elimination of propofol.

PROPOFOL has been widely used for anesthesia during surgical procedures and for sedation of patients. It is a short-acting drug with a large volume of distribution and a high total body clearance.<sup>1</sup> Because the hepatic extraction ratio of propofol is very high<sup>2</sup> and the urinary excretion of unchanged propofol is very little,<sup>1</sup> hepatic metabolism is considered as the main elimination pathway of propofol. However, total body clearance of propofol exceeds liver blood flow,<sup>1,3</sup> suggesting a contribution of extrahepatic clearance. Veroli *et al.*<sup>4</sup> reported the presence of propofol metabolites in urine after a single intravenous bolus dose of propofol at the anhepatic phase. It remains uncertain which organs contribute to the extrahepatic clearance of propofol, although organs receiving a significant proportion of the total cardiac output (*e.g.*, lungs, brain, kidneys) would be likely candidates to have large clearance.

Extensive first-pass elimination of propofol at the lungs of sheep, cats, and rats have been reported.<sup>5-8</sup> However, the role of the lungs for the metabolism of propofol in humans is controversial.<sup>9,10</sup> Glucuronidation is the major metabolic pathway of propofol in humans,<sup>1,11</sup> and UDP-glucuronosyltransferase isoforms are expressed in the kidney and brain.<sup>12-16</sup> However, the contribution of the kidneys to the clearance of propofol *in vivo* remains unclear.

The purpose of this study was to perform a quantitative evaluation of the role of the kidneys as an extrahepatic site of propofol disposition. Renal blood flow and renal extraction ratio of propofol were directly measured to determine the proportion of renal clearance in total body clearance.

## Materials and Methods

### Subjects

After institutional approval (Graduate School of Medicine, Gunma University, Showa-machi, Maebashi, Japan), informed consent was obtained from 10 patients undergoing nephrectomy under the diagnosis of renal cell carcinoma (5 right and 5 left nephrectomy; 8 males and 2 females; age, 66 ± 9.2 yr; height, 165 ± 7.7 cm; weight, 64 ± 7.8 kg). Individuals who had severe hepatic insufficiency, significant hemodynamic instability, or a known allergy to eggs, propofol, or *para*-aminohippurate (PAH) were excluded from the study.

### Sampling Procedure

Before induction of anesthesia, 3 ml blood was taken to obtain a blank sample of plasma for the measurement of PAH. Thereafter, 5% PAH infusion was started at a rate of 30 ml/h for the initial 5 min and 10 ml/h until the end of the operation. Anesthesia was induced with vecuronium (0.1 mg/kg) and propofol (2 mg/kg) and then maintained with nitrous oxide (60%) and sevoflurane (1~2%) in oxygen with an infusion of propofol (2 mg · kg<sup>-1</sup> · h<sup>-1</sup>). Blood samples were collected from a cannula inserted in the radial artery every 30 min. Because it has been reported that the concentration of propofol reached more than 85% of the final steady state value,<sup>3</sup> the level of propofol at least 2 h after the start of constant infusion was regarded as steady state. The renal venous blood was obtained immediately after the ligation of the renal vein for nephrectomy. At the same time, the radial arterial blood was also obtained. Because we could not obtain a blood sample from the renal vein of the other side, the extraction ratio of both sides of the

\* Instructor Anesthetist, Departments of Anesthesiology and Clinical Pharmacology, † Instructor Anesthetist, ‡ Professor, Department of Anesthesiology, § Assistant Professor, || Professor, Department of Clinical Pharmacology, Graduate School of Medicine, Gunma University.

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Address reprint requests to Dr. Horiuchi: Department of Clinical Pharmacology, Graduate School of Medicine, Gunma University Graduate School of Medicine, 3-39-22, Showa-machi, Maebashi 371-8511, Japan. Address electronic mail to: horiuchi@med.gunma-u.ac.jp. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

kidney was assumed to be the same. After ligation of the renal vein, blood samples of the radial artery were collected every 30 min in the same way until the end of the operation.

#### *Measurement of Plasma Unbound Fraction by Equilibrium Dialysis*

Unbound fraction of propofol to arterial plasma protein was estimated using equilibrium dialysis method. Plasma samples (1 ml each) were dialyzed against an isotonic buffer containing 0.067 M sodium phosphate and 0.05 M sodium chloride (pH 7.4) for 10 h at 37°C using a dialysis membrane with a molecular weight cut-off of 6,000 (VB-8, Sanplatec, Japan). In the preliminary experiments, the concentrations of propofol in both sides of the dialysis membrane reached equilibrium after 5 h, and 80% of the added amount of propofol was recovered after dialysis. After dialysis, the propofol concentrations in the plasma and the dialyzed fractions were analyzed separately. The unbound fractions of propofol in plasma ( $f_u$ ) and blood ( $f_B$ ) were calculated according to the following equations:

$$f_u(\%) = \frac{\text{concentration in buffer fraction}}{\text{concentration in plasma fraction}} \times 100$$

$$f_B(\%) = \frac{f_u \times \text{plasma concentration of propofol at steady state}}{\text{whole blood concentration of propofol at steady state}}$$

#### *Analytical Procedure*

Five milliliters heparinized blood was centrifuged immediately, and then obtained plasma samples were stored at -20°C until subsequent analysis. The plasma concentration of PAH was measured using the method of Brun.<sup>17</sup>

The propofol concentrations in whole blood from artery and renal vein, plasma from artery, and dialysate and retentate after dialysis were measured using high-performance liquid chromatography as reported previously.<sup>2</sup>

#### *Measurement of Renal Blood Flow*

Renal plasma flow (RPF) was determined by the steady state infusion and extraction technique using PAH as an indicator. RPF and renal blood flow (RBF) were calculated by equations 1 and 2, respectively.

$$\text{RPF} = \frac{\text{infusionrate}}{(\text{Ca,PAH} - \text{Cv,PAH})} \quad (1)$$

$$\text{RBF} = \text{RPF} \times 100 / (100 - \text{Ht}), \quad (2)$$

where  $\text{Ca,PAH}$  and  $\text{Cv,PAH}$  are the steady state concentrations of PAH in plasma at the radial artery and renal vein, respectively.

#### *Calculation of Propofol Clearance*

The renal extraction ratio of propofol ( $E(r)$ ) was calculated as

$$E(r) = (\text{Ca,pro} - \text{Cv,pro}) / \text{Ca,pro}, \quad (3)$$

where  $\text{Ca,pro}$  and  $\text{Cv,pro}$  are the steady state concentrations of propofol in whole blood in the radial artery and renal vein, respectively.

The total body clearance ( $\text{Cl}_{\text{tot}}$ ) and renal clearance ( $\text{Cl}_r$ ) of propofol were calculated as follows:

$$\text{Cl}_{\text{tot}} = \text{infusionrate} / \text{Ca,pro} \quad (4)$$

$$\text{Cl}_r = \text{RBF} \times E(r). \quad (5)$$

Usually, renal clearance of a drug is expressed as the sum of glomerular filtration, tubular secretion, and reabsorption. However, most of propofol is eliminated by renal metabolism, and only 0.3% of propofol is excreted in urine in unchanged form.<sup>1</sup> Therefore, the renal intrinsic clearance of propofol ( $\text{Cl}_{\text{int,r}}$ ) was calculated using a formula similar to that for hepatic intrinsic clearance.

$$\text{Cl}_r = \text{RBF} \times \text{Cl}_{\text{int,r}} \times f_B / (\text{RBF} + \text{Cl}_{\text{int,r}} \times f_B), \quad (6)$$

where  $f_B$  is the unbound fraction of propofol in blood.

#### *Statistical Analysis*

Data are expressed as mean  $\pm$  SD. The differences in propofol concentrations between the radial artery and the renal vein were analyzed by paired  $t$  test. The differences in propofol concentration and renal blood flow before and after removal of the kidney were analyzed by paired  $t$  test. A  $P$  value of less than 0.05 was considered statistically significant.

## Results

All patients tolerated the surgery without complications and were clinically improved at the time of discharge from hospital. Ligation of the renal vein for nephrectomy was performed at  $2.47 \pm 0.34$  h (mean  $\pm$  SD; range, 2.1–3.1 h) after the start of the continuous infusion of propofol.

The propofol concentration in the radial artery ( $1.43 \pm 0.18$   $\mu\text{g/ml}$ ) was higher than in the renal vein ( $0.60 \pm 0.21$   $\mu\text{g/ml}$ ) ( $P < 0.0001$ ; table 1). The renal extraction ratio of propofol was  $0.58 \pm 0.15$ .

Total body clearance was  $1.53 \pm 0.25$  l/min. The renal clearance of propofol just before binding the renal artery was  $0.41 \pm 0.15$  l/min, or  $27 \pm 9.9\%$  of total body clearance. The unbound fraction of propofol in blood was  $0.024 \pm 0.0084$ , and renal intrinsic clearance was  $73 \pm 79$  l/min.

Although renal blood flow decreased from  $0.74 \pm 0.15$  l/min to  $0.51 \pm 0.11$  l/min ( $P < 0.0001$ ) after the ligation of the renal artery for nephrectomy, there was no significant change of propofol concentration in blood from the radial artery ( $P = 0.19$ ; fig. 1).

**Table 1. Propofol Concentration in Blood Taken from the Radial Artery and Renal Vein and Renal Extraction Ratio of Propofol**

Patient No.	Ca, $\mu\text{g/ml}$	Cv, $\mu\text{g/ml}$	E(r)
1	1.5	0.81	0.47
2	1.2	0.42	0.67
3	1.7	0.22	0.87
4	1.3	0.31	0.77
5	1.7	0.71	0.58
6	1.5	0.78	0.47
7	1.4	0.82	0.43
8	1.5	0.64	0.57
9	1.3	0.71	0.45
10	1.2	0.62	0.48
Mean	1.43	0.60	0.58
SD	0.18	0.21	0.15

Ca = propofol concentration in blood taken from the radial artery; Cv = propofol concentration in blood taken from the renal vein; E(r) = renal extraction ratio of propofol.

## Discussion

The pharmacokinetics of propofol have been studied in healthy subjects<sup>18,19</sup> and groups of patients with renal<sup>20</sup> and hepatic insufficiency.<sup>21</sup> Propofol was extensively distributed and rapidly cleared from the body in each condition. Extrahepatic clearance of propofol has been suggested because total body clearance exceeds hepatic blood flow. We have directly demonstrated the disappearance of propofol in the kidneys.

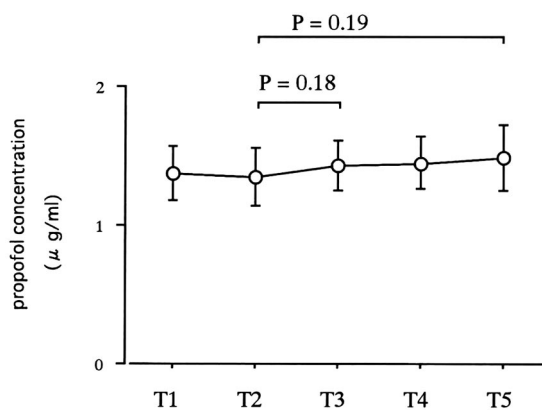
Glucuronidation is the major metabolic pathway of propofol in humans.<sup>1,11</sup> Raof *et al.*<sup>16</sup> reported that human liver, kidney, and small intestine were capable of forming propofol glucuronide. In the current study, we showed that renal clearance of propofol was  $0.41 \pm 0.15$  l/min, or  $27 \pm 9.9\%$  (mean  $\pm$  SD) of total body clearance. Therefore, it became clear that the human

kidneys play an important role in the elimination of propofol.

Icks *et al.*<sup>20</sup> reported that total body clearance of propofol was similar in individuals with end-stage renal disease and control subjects. They concluded that the kidneys do not contribute significantly to the extrahepatic clearance of propofol. However, a considerable amount of propofol disappeared in the human kidneys. Usually, renal clearance of a drug is expressed as the sum of glomerular filtration, tubular secretion, and reabsorption. However, most of propofol is eliminated as metabolites, and only 0.3% of propofol is found as unchanged form in urine.<sup>1</sup> Therefore, renal intrinsic clearance of propofol (Cl<sub>int,r</sub>) could be calculated using a formula similar to that for hepatic intrinsic clearance. In this study, renal intrinsic clearance of propofol was calculated as  $73 \pm 79$  l/min. The product of renal intrinsic clearance and the unbound fraction in blood was  $1.48 \pm 1.24$  and exceeded renal blood flow ( $0.74 \pm 0.15$  l/min). It might be considered that renal intrinsic clearance is so high that the renal clearance of propofol depends on renal blood flow and is unaffected by renal failure.

After nephrectomy, renal blood flow decreased by one third. If 27% of total body clearance were renal, total body clearance was expected to reduce by 9% after nephrectomy. Such a small difference in clearance rate is difficult to detect. We found no significant difference in total body clearance of propofol before and after nephrectomy. Although the kidneys are an important site of propofol elimination, our results suggest that total body clearance is not appreciably influenced by nephrectomy. Therefore, propofol can be used safely for patients undergoing nephrectomy.

In this study, renal extraction ratio and total body clearance of propofol was calculated at the pseudo-steady state—at least 2 h after the start of continuous infusion. We cannot entirely rule out the possibility that the apparent clearance of propofol in the kidneys results from a distribution of the drug into tissues, which would tend to overestimate total body clearance. True steady state was not established during this study because the elimination half-life of propofol is quite long (4–6 h). However, given that the rapid distribution half-life is short (1–3 min) and the distribution clearance is large,<sup>22,23</sup> the concentration of propofol reaches pseudo-steady state at 20 min after a constant infusion and increases slowly until true steady state is reached.<sup>9</sup> The contribution of rapid distribution, second elimination (30–50 min), and terminal elimination half-life (4–6 h) to the changes in concentration are 94.6, 4.9, and 0.57%, respectively.<sup>24</sup> There is a slight contribution of terminal half-life to the increase in concentration of propofol, but this is probably clinically irrelevant. Therefore, the pseudo-steady state of propofol is almost equal to the true steady state. Propofol concentrations were reasonably stable (fig. 1). Furthermore, the distribution process of



**Fig. 1.** The transition of propofol concentrations during nephrectomy. T1 and T2 represent 1 h and 2 h from the beginning of the infusion, respectively. T3 represents a mean of  $2.47 \pm 0.34$  h (mean  $\pm$  SD) at the time of ligation of renal vein. T4 and T5 represent 1 h and 2 h from the time of ligation of renal vein, respectively. T3 and T5 were assumed to be the steady state before and after nephrectomy, respectively.

propofol into well-perfused organ tissue, such as the lungs, reaches equilibrium within a short time of constant infusion.<sup>9</sup> In contrast, less well-perfused organs, such as fat, approach steady state conditions quite slowly. Therefore, we believe that renal extraction of propofol at pseudo-steady state does not reflect distribution.

In conclusion, human kidneys play an important role in the elimination of propofol. The renal intrinsic clearance is so high that the renal clearance of propofol depends on renal blood flow. Total body clearance of propofol is not significantly influenced by nephrectomy.

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