Do the kidneys contribute to propofol elimination?

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Background. Propofol is mainly metabolized in the liver, but extrahepatic clearance may also be important since systemic propofol clearance exceeds hepatic clearance. Recent reports suggest that the kidneys contribute to propofol elimination in humans and here we investigated renal elimination of propofol in a controlled animal study.

Methods. Seventeen swine were anaesthetized with 5% isoflurane induction and 2% isoflurane maintenance. After a left subcostal incision, the left kidney and renal pedicle were exposed by an approach via the retroperitoneum and the renal vein was identified for blood sampling. Propofol was then administered via the right jugular vein at a rate of 2 mg kg\(^{-1}\) h\(^{-1}\). After 120 min of pseudo-steady-state infusion of propofol (Baseline 1), cardiac output (CO) was increased by continuous infusion of dobutamine for 30 min (high-CO state). Thirty minutes after stopping dobutamine (Baseline 2), CO was decreased by bolus administration of propranolol (low-CO state). Blood samples were collected simultaneously from the renal vein (direct puncture) and the femoral artery at Baseline 1, in the high-CO state, at Baseline 2, and in the low-CO state.

Results. There was no significant difference in propofol concentration between femoral arterial and renal venous blood in all states. The propofol concentration significantly decreased with increased CO, but renal extraction was not observed in any state.

Conclusions. The kidneys are a minor site of propofol elimination in a swine model.

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Propofol is widely used as an agent for induction and maintenance of general anaesthesia and sedation in the intensive care unit. Glucuronidation in the liver is the main metabolic pathway; however, extrahepatic clearance has also been considered because systemic propofol clearance exceeds the generally accepted estimate for liver blood flow\(^{1–7}\) and a propofol metabolite in urine has been detected during the anhepatic phase in humans.\(^{8}\) Furthermore, a recent animal study demonstrated that the arterial blood concentration did not change markedly during the anhepatic phase.\(^{9}\) These observations have led to an investigation of which organs contribute to extrahepatic clearance.

The lungs have historically been thought to play an important role in clearance of many drugs, but several reports suggest that the lungs are not a major site contributing to extrahepatic metabolism of propofol.\(^{7,10}\) It has recently been suggested that the kidneys contribute to propofol elimination; Takizawa and colleagues\(^{11}\) found that the renal extraction ratio (ER) of propofol was approximately 50–70% in humans,\(^{12}\) suggesting that the kidneys are a major organ responsible for extrahepatic metabolism in humans.

The objective of the current study was to investigate renal elimination of propofol in various cardiac output (CO) states associated with different systemic clearance\(^{13–16}\) in anaesthetized swine. To increase the accuracy of the study, the renal vein was punctured to allow direct collection of blood samples.

Methods

Animal preparation

This study was approved by the local institutional ethics committee (Committee on Animal Research, Hamamatsu University School of Medicine, Hamamatsu, Japan). Seventeen swine [body weight range, 24.3–35.7 kg; mean...
Propofol elimination in the kidneys

Experimental protocol

After completion of animal preparation, propofol was administered with an infusion pump (TE-312; Terumo, Tokyo, Japan) via a central catheter at a rate of 2 mg kg\(^{-1}\) h\(^{-1}\). Similar to our previous report, we chose low-dose propofol infusion under sufficient isoflurane anaesthesia instead of high-dose propofol as a single agent, because in our pilot studies it was difficult to maintain haemodynamic stability and a stable anaesthetic depth, even with a relatively high dose of propofol. We believe that this is an acceptable method for evaluation of propofol elimination. To measure steady-state plasma propofol concentration, 2 ml blood samples were collected simultaneously from the renal vein (direct puncture using 25 gauge needles) and femoral artery in each of the following haemodynamic states: 120 min after the start of propofol infusion (Baseline 1); in a high-CO state induced by 40 min of continuous infusion of dobutamine at a rate of 20 \(\mu g\) kg\(^{-1}\) min\(^{-1}\) (high-CO state); at a second baseline 40 min after stopping dobutamine infusion (Baseline 2); and in a low-CO state induced by bolus administration of 2.0–4.0 mg propranolol (low-CO state). Blood samples in the high-CO state, at Baseline 2, and in the low-CO state were collected after ensuring haemodynamic stability for 40 min after starting dobutamine infusion, after stopping dobutamine infusion, and after bolus administration of propranolol, respectively.

After haemodynamic stability was achieved and maintained for at least 10 min, CO values were measured by the thermodilution method just before blood sampling in each state. CO was determined with a thermodilution computer (Cardiac Output Computer, MTC6210; Nihon Kohden, Tokyo, Japan) using 5 ml of cold 5% glucose injected into the right atrium. The indicator for thermodilution was administered by the same person during apnoea at the end of expiration. Each CO value was measured four times and the mean of the last three values was recorded. These methods were based on those used in our previous study. Blood gases, haematocrit, lactate concentrations, and plasma osmolality of femoral arterial blood and renal venous blood were analysed immediately after collection.

Blood-plasma samples were immediately separated and stored at 5°C on ice until extraction and assay. Within 12 h of sampling, propofol concentrations were assayed by high-performance liquid chromatography (HPLC) with fluorescent detection at 310 nm after excitation at 276 nm (CTO-10A, RF550, and C-R7A; Shimadzu, Kyoto, Japan), following the method of Plummer. The lower limit of detection was 15 ng ml\(^{-1}\) and the mean intra-assay coefficient of variation was 2.1%.

Statistical analysis

Data are expressed as means (sd). HR, MAP, mean pulmonary arterial pressures (MPAP), central venous pressures (CVP), COs, propofol concentrations, and renal ER for each haemodynamic state were analysed by repeated-measures one-way analysis of variance (ANOVA). Blood samples from the femoral artery and renal vein in each haemodynamic state (Table 1) were analysed using an unpaired \(t\)-test. Differences in propofol concentrations between the femoral artery and the renal vein in each haemodynamic state were analysed using two-way ANOVA. If the ANOVA was found to be significant, a Scheffé \(F\)-test was performed to compare the difference in values. \(P<0.05\) was considered to be statistically significant.

Results

Femoral arterial and renal venous blood analysis data are shown in Table 1 with haemodynamic variables for each state shown in Table 2. The lack of significant differences in haematocrit and plasma osmolality between the artery and the vein (Table 1) indicates that there was no experimental contamination. Arterial \(P_{aO2}\) was higher than venous \(P_{aO2}\), and HR changed significantly after all changes to CO status. The MAP was lower in the high-CO state than at Baseline 1, probably because the high-dose dobutamine infusion induced systemic vasodilatation. CO significantly increased in the high-CO state and significantly decreased in the low-CO state when compared with Baselines 1 and 2.
Changes in CO and plasma propofol concentrations in the femoral artery and renal vein at each state are shown in Figure 1. Femoral arterial propofol concentrations at Baseline 1, in the high-CO state, at Baseline 2, and in the low-CO state were 0.00 (9.03), 7.9 (4.2), 2.4 (1.3), and 1.10 (0.26) mmol litre$^{-1}$, respectively; the plasma propofol concentrations in the femoral artery and the plasma propofol concentration in the renal vein significantly lower than those in the other three haemodynamic states ($P<0.0001$). There were no significant differences ($P=0.3055$) between the plasma propofol concentration in the femoral artery and the plasma propofol concentration in the renal vein in any haemodynamic state.

Renal propofol ER is shown in Figure 2, and was calculated as follows: $100 \times \frac{\text{plasma propofol concentration in the femoral artery} - \text{plasma propofol concentration in the renal vein}}{\text{plasma propofol concentration in the femoral artery}}$ (\%). The renal ER of propofol at Baseline 1, in the high-CO state, at Baseline 2, and in the low-CO state were 0.38 (7.79), 7.80 (10.39), and 4.60 (11.58), respectively; that is, the ER was not dependent on haemodynamic changes.

Discussion

The results of this study indicate no apparent renal extraction of propofol at any CO state, providing the first evidence that the kidneys are a minor site contributing to extrahepatic propofol elimination. Renal ER was investigated in various CO states inducing different levels of systemic clearance. CO significantly increased by 44% [high-CO=5.27 (1.15) litre min$^{-1}$] from Baseline 1 [CO=3.67 (0.78) litre min$^{-1}$] and significantly decreased by 29% [low-CO=2.62 (0.64) litre min$^{-1}$] from Baseline 2 [CO=3.67 (0.62) litre min$^{-1}$]. With these respective haemodynamic changes, the plasma propofol concentration decreased by 31% [0.74 (0.26) µg ml$^{-1}$], but did not change significantly in the low-CO state [1.10 (0.26) µg ml$^{-1}$]. This was probably because CO did not decrease sufficiently to increase the propofol concentration. As we have reported previously, CO of 2 litre min$^{-1}$ is a boundary point in our swine model: at CO $\leq$ 2 litre min$^{-1}$, the
Propofol concentration increases significantly, but at CO >2 litre min⁻¹, the increase in propofol concentration relative to the decrease in CO is not significant.¹⁸

In this animal study, we did not measure hepatic blood flow, but systemic clearance was 0.94 litre min⁻¹, which is similar to that in our previous work (0.91 litre min⁻¹), in which liver blood flow was <0.5 litre min⁻¹.¹⁷ In a human study, Lange and colleagues¹⁹ reported systemic propofol clearance of 2.39 litre min⁻¹ and hepatic propofol clearance of 1.06 litre min⁻¹. These findings suggest that approximately half of propofol clearance depends on extrahepatic routes in both humans and swine.¹—⁷ Recently, in human studies, Takizawa and colleagues¹¹ ¹² ²⁰ investigated the elimination of propofol by the kidneys, small intestine, brain, and lungs and showed that the kidneys are particularly important for propofol elimination. However, renal elimination of propofol was not observed in our animal study, in contrast to the results of these human studies.¹¹ ¹² The discrepancy between these studies may be due to the different methods of blood collection. Takizawa and colleagues¹¹ collected blood samples simultaneously from the radial artery and renal vein after ligation of the renal artery in patients undergoing nephrectomy, and Hiraoka and colleagues¹² collected blood samples simultaneously from the radial artery and renal vein via a catheter inserted into the right renal vein under fluoroscopic and ultrasonic guidance in patients undergoing cardiac surgery with cardiopulmonary bypass. In our study, renal blood flow was completely preserved by maintaining a normal heart beat, and direct puncture of the renal vein was used to avoid contamination with exudate and blood from the inferior vena cava. In fact, based on the absence of significant differences in haematocrit and plasma osmolality in the artery and vein, there was little contamination. We also note that the variation in the renal ER in our study was smaller than that in the human studies.

Several limitations of this study need to be addressed. Our results were negative, but the power of the present study is less than 80% to accept the null hypothesis with certainty; therefore, a type II error cannot be excluded. Furthermore, we cannot exclude the possibility that concomitant administration of isoflurane might influence organ metabolism. Also, CO may have changed as a result of high concentrations of dobutamine and propranolol, and these drugs might impose stress on the liver and other extrahepatic organs. Finally, we did not measure the level of the propofol metabolite, 2,6-disopropyl-1,4-quinol, making it difficult to conclude with certainty that propofol is not metabolized in the kidneys. In fact, although Dawidowicz and colleagues²¹ have reported that propofol is metabolized in human lungs, based on measurements of propofol metabolites, we have previously concluded that the lungs are only a minor site contributing to extrahepatic elimination of propofol in anaesthetized swine,⁷ and similarly He and colleagues¹⁰ have demonstrated that human lungs do not metabolize propofol. At least, we can conclude from the present study that the kidneys are only a minor contributor to extrahepatic elimination of propofol in anaesthetized swine, and that extraction of propofol by the kidneys is minimal in the pseudo-steady state and is unrelated to CO. Despite the species difference, it is noteworthy that a controlled animal study gave results that are inconsistent with recent human studies, and further human work might be necessary to determine the importance of renal elimination and metabolism of propofol.

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