

The Role of Human Lungs in the Biotransformation of Propofol

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Background: **The metabolism of propofol is very rapid, and its transformation takes place mainly in the liver. There are reports indicating extrahepatic metabolism of the drug, and the alimentary canal, kidneys, and lungs are mentioned as the most probable places where the process occurs. The aim of this study was to determine whether the human lungs really take part in the process of propofol biotransformation.**

Methods: **Blood samples were taken from 55 patients of American Society of Anesthesiologists grade 1–3 scheduled for elective intracranial procedures (n = 47) or for pulmonectomy (n = 8). All patients were premedicated with diazepam (10 mg) administered orally 2 h before anesthesia. Propofol total intravenous anesthesia was performed at the following infusion rates: 12 mg · kg^{-1} · h^{-1}, 9 mg · kg^{-1} · h^{-1}, and 6 mg · kg^{-1} · h^{-1}. Fentanyl and pancuronium bromide were also administered intermittently. After tracheal intubation, the lungs were ventilated to normocapnia with an oxygen–air mixture (fraction of inspired oxygen = 0.33). Blood samples for propofol and 2,6-diisopropyl-1,4-quinol analysis were taken simultaneously from the right atrium and the radial artery, or the pulmonary artery and the radial artery. The concentration of both substances were measured with high-performance liquid chromatography and gas chromatography–mass spectroscopy.**

Results: **The concentration of propofol in the central venous system (right atrium or pulmonary artery) is greater than in the radial artery, whereas the opposite is observed for propofol's metabolite, 2,6-diisopropyl-1,4-quinol. Higher propofol concentrations are found in blood taken from the pulmonary artery than in the blood collected from the radial artery.**

Conclusions: **Human lungs take part in the elimination of propofol by transforming the drug into 2,6-diisopropyl-1,4-quinol. (Key words: Pulmonary metabolism.)**

PROPOFOL metabolism in human organism, which is considered to be both hepatic and extrahepatic,[1–3] has not been fully defined. Some reports suggest that the lungs play an essential role in the process of clearing the drug.[4–6] Although more and more reports show the importance of the lungs in the drug metabolism process, the role of this organ in relation to propofol has not been fully determined; moreover, some descriptions of the behavior of propofol in humans are contradictory.[4–9] The aim of this study was to determine whether the lungs take part in the biotransformation process of propofol in humans. The veno-arterial differences of propofol and its metabolite, 2,6-diisopropyl-1,4-quinol, concentrations across the human lungs are discussed.

Materials and Methods

Blood Sampling

After obtaining approval from the University Ethical Committee and consent from patients, samples were taken from 55 patients of American Society of Anesthesiologists grade 1–3. Two groups of patients were studied: (1) group I: 47 patients (26 women and 21 men; age, 45 ± 14 yr; weight, 70 ± 13 kg) scheduled for elective intracranial procedures; and (2) group II: 8 patients (2 women and 6 men; age, 60 ± 8 yr; weight, 65 ± 3 kg) scheduled for pulmonectomy.

All patients were premedicated with diazepam (Polfa, Warszawa, Poland) 10 mg administered orally 2 h before anesthesia. Before induction, the patients received a bolus dose of fentanyl (Polfa) 0.2 mg and were preoxygenated with 100% oxygen for 10 min. Propofol (Diprivan; AstraZeneca, Caponago, Italy) was first injected as a bolus dose (2 mg/kg) and then continuously infused. The following infusion rates were used[10,11]: 12 mg · kg^{-1} · h^{-1} for the first 15 min, 9 mg · kg^{-1} · h^{-1} for the next 25 min, and 6 mg · kg^{-1} · h^{-1} thereafter. Endotracheal intubation was facilitated by pancuronium bromide (Organon Teknika, Boxtl, Holandia) 0.05 mg/kg. After tracheal intubation, the lungs were ventilated to normocapnia with an oxygen–air mixture (fraction of inspired oxygen = 0.33). In addition to the continuous infusion of propofol, anesthesia was maintained with repeated doses of fentanyl and pancuronium. The infusion of propofol was stopped immediately after the surgical procedure. Neuromuscular block was antagonized with atropine (Polfa; 0.5 mg) and neostigmine bromide (Pliwa, Kraków, Poland; 2.5 mg).

Before induction of anesthesia, a 17-gauge cannula was inserted in the large vein of left forearm and was used solely for the infusion of propofol. After induction of anesthesia, two additional cannulas were placed: one (20-gauge) in the radial artery in the contralateral forearm (for blood pressure monitoring and blood sampling), and the other (7 French × 20) in the right subclavian vein (for central venous pressure measurement and blood sampling). The position of the cannula was localized in the right atrium by radiograph.

In group I, blood samples were collected simultaneously from the right atrium and radial artery (venous blood and arterial blood) 90 min after the induction

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of anesthesia, when the rate of propofol infusion was 6 $mg \cdot kg^{-1} \cdot h^{-1}$. In addition, a second pair of samples was taken from 31 of 55 patients 20 min after termination of propofol infusion. In 60 pairs of blood samples (36 collected during infusion, 24 collected after infusion), the concentration of propofol was determined by high-performance liquid chromatography (HPLC). In the remaining samples, the levels of propofol and its metabolite, 2,6-diisopropyl-1,4-quinol, were estimated by gas chromatography–mass spectroscopy.

In group II, samples were taken simultaneously from the pulmonary and radial arteries (mixed venous blood and arterial blood) just before the removal of the lung; time of sampling was 117 ± 28 min after the beginning of propofol infusion. Propofol concentrations were measured by HPLC.

Reagents and Solutions

All chemicals used, except those mentioned separately, were obtained from the Polish Factory of Chemical Reagents-POCh (Gliwice, Poland) and were of analytical grade. A mixture of 67% acetonitrile and 33% double-distilled water (pH 2.0) was used as mobile phase. The desired pH was achieved by the addition of trifluoracetic acid (1 ml acid to 400 ml water). Propofol was obtained from ICI-Pharma (Goteborg, Sweden). Stock solutions of thymol and propofol in acetonitrile (1 mg/ml) were each prepared and stored at 4°C. Tetramethylammonium hydroxide (25% in methanol; Aldrich, Steinheim, Germany) was diluted with 2-propanol (3:37). Trifluoroacetic acid was purchased from Fluka (Buchs, Switzerland).

Extraction Procedure

Thymol, phosphate buffer (1 ml of 0.1 M NaH_2PO_4, pH 4.2) and cyclohexane (5 ml) were added to the samples of blood. The samples were vigorously shaken for 15 min. After centrifugation (1,200*g* for 5 min), an aliquot of the cyclohexane layer (4.5 ml) was transferred to a clean tube to which tetramethylammonium hydroxide solution (20 μl) was subsequently added. The solvent was evaporated to dryness with a stream of nitrogen. The residue was redissolved in the mobile phase and injected into the chromatographic column.

High-performance Liquid Chromatography Analysis

A Gilson liquid chromatograph (Middleton, WI) consisting of two high-pressure pumps (Models 305 and 306), a Model 805 manometric module, and a Model 811 C dynamic mixer were used. The ultraviolet–visible variable wavelength detector working at 270 nm was a Model 119 (Gilson). Chromatographic separations were conducted using a 250 × 4 mm ID column packed with homemade C18 silica gel. The samples (20 μl) were injected into the column by a Model 7125 injection valve (Rheodyne, Cotati, CA). The intraday and interday relative recovery was 100% with a coefficient of variation (C_V) < 6%. The limit of sensitivity of the assay was 0.1 μg/ml.

Gas Chromatography–Mass Spectroscopy Analysis

The analyses were performed on gas chromatography–mass spectroscopy with an ion trap (ITS-40; Finnigan MAT, San Jose, CA). The samples (2 μl) were injected into a DB-5 (J&W, Folson, CA) fused silica capillary column (30 m × 0.25 mm ID; 0.25-μm film thickness) by splitless injection. The temperature program was as follows: isotherm 40°C (2 min), temperature program 8°C/min to 230°C, temperature program 25°C/min to 300°C, and final isotherm 300°C (5 min). Helium as carrier gas with the flow of 1.5 ml/min was used. Mass spectroscopy conditions were as follows: electron impact (70 eV); manifold temperature, 220°C; mass range, 35–400 atom unit mass. At the absence of an authentic metabolite standard, quantitative analysis was performed on the basis of the extracted ion chromatograms with total ion current for propofol, 2,6-diisopropyl-1,4-quinol, and thymol, which was used as an internal standard. The number of ions is proportional to the concentration of the corresponding compounds in blood.

The precision of the assay was found to have a C_V less than 5.5%, and the accuracy expressed by the relative recovery was 100%.

Calibration Procedure for High-performance Liquid Chromatography Measurements

Standard solutions of propofol with thymol were prepared in blood. Using this set of solutions and following the described extraction procedure and HPLC analysis, the ratios of the peak area of propofol to thymol (A_P/A_T) were plotted against the concentration of propofol in blood.

The concentration of propofol in the examined samples was calculated using the regression parameters obtained from the calibration curves by means of UniPoint System Software (Gilson, Middleton, WI).

Statistical Analysis

The data are expressed as mean value ± SD. The differences between blood vessels in relation to propofol and 2,6-diisopropyl-1,4-quinol were compared with the Student *t* test for dependent samples. The comparison of ratios between propofol and 2,6-diisopropyl-1,4-quinol was analyzed by the Wilcoxon matched-pairs test. Differences were considered significant at *P* less than 0.05.

Results

Data for group I, the propofol concentrations determined for the blood samples taken simultaneously from the right atrium and the radial artery (venous blood and arterial blood) by means of HPLC, are presented in fig. 1.

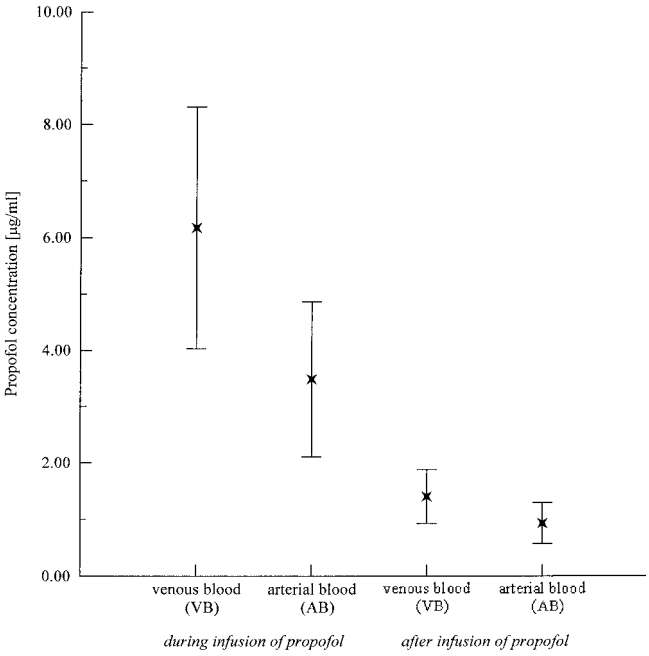

Fig. 1. Propofol concentration in blood taken from the right atrium (venous blood; C_{VB}) and from radial artery (arterial blood; C_{AB}) during infusion (n = 36) and after termination of infusion (n = 24) for group I measured by HPLC.

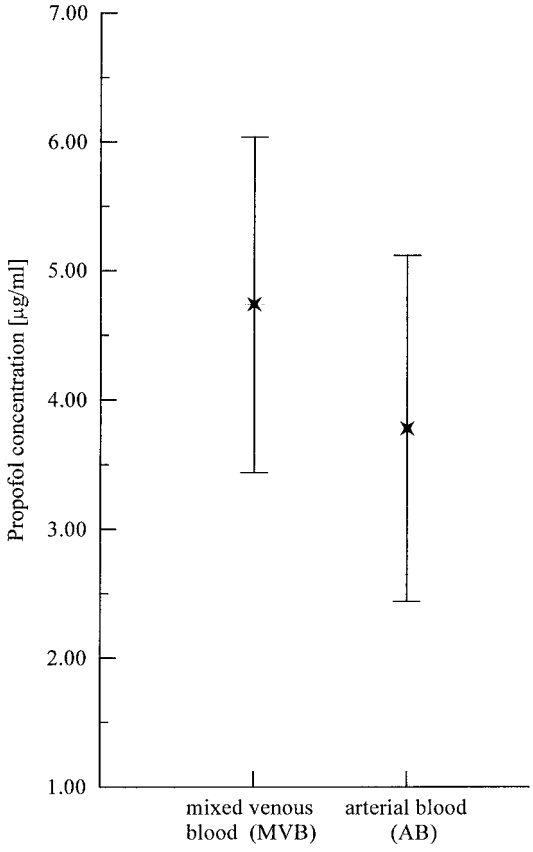

Fig. 2. Propofol concentration in blood taken from pulmonary artery (mixed venous blood; C_{MVB}) and from radial artery (arterial blood; C_{AB}) for group II (n = 8).

The higher propofol concentration in blood from the right atrium than from the radial artery is observed both during propofol infusion (6.17 ± 2.15 μg/ml and 3.49 ± 1.38 μg/ml, $P < 0.001$) and after termination of infusion (1.41 ± 0.48 μg/ml and 0.93 ± 0.36 μg/ml, $P < 0.001$). The mean veno-arterial differences and ratios of concentrations are shown in table 1.

The results of measurements of propofol concentration for group II performed in blood samples collected simultaneously from the pulmonary artery and the radial artery (mixed venous blood and arterial blood) are shown in figure 2. The higher propofol concentration is observed in mixed venous blood than in arterial blood (4.74 ± 1.30 μg/ml and 3.78 ± 1.34 μg/ml, $P < 0.005$).

The levels of propofol and 2,6-diisopropyl-1,4-quinol for group I determined by gas chromatography–mass spectroscopy in blood samples taken simultaneously from the right atrium and the radial artery (venous blood and arterial blood) expressed by the total number of ions are presented in figures 3 and 4. Both during propofol infusion (fig. 3) and after termination of infusion (fig. 4) the propofol level is higher in venous blood than in arterial blood ($P < 0.001$), whereas the level of 2,6-diisopropyl-1,4-quinol is higher in blood from the radial artery than from the right atrium ($P < 0.01$).

Table 1. Veno-arterial Concentration Differences Expressed in μg/ml or Total Ion Numbers and Veno-arterial Concentration Ratios for Propofol (p) and 2,6-diisopropyl-1,4-quinol (q)

No.	Group	Blood Sampling during or after Infusion	Compound	Figure No. Presenting the Data	Veno-arterial Concentration Differences	Veno-arterial Concentration Ratios
1	I	During	p	1	2.68 ± 1.18 μg/ml*	1.82 ± 0.39*
2	I	After	p	1	0.48 ± 0.33 μg/ml*	1.58 ± 0.44*
3	II	During	p	2	0.97 ± 0.51 μg/ml†	1.33 ± 0.35†
4	I	During	p	3	16,264,952 ± 8,885,934 number of ions*	1.77 ± 0.37*
5	I	During	q	3	50,752 ± 50,787 number of ions‡	1.81 ± 0.59‡
6	I	After	p	4	3,079,477 ± 1,361,392 number of ions*	1.50 ± 0.25*
7	I	After	q	4	16,204 ± 11,016 number of ions‡	1.36 ± 0.22‡

* $C_{VB} - C_{AB}$ and C_{VB}/C_{AB}.

† $C_{MVB} - C_{AB}$ and C_{MVB}/C_{AB}.

‡ $C_{AB} - C_{VB}$ and C_{AB}/C_{VB}.

C_{VB} = propofol concentration in venous blood; C_{AB} = propofol concentration in arterial blood; C_{MVB} = propofol concentration in mixed venous blood.

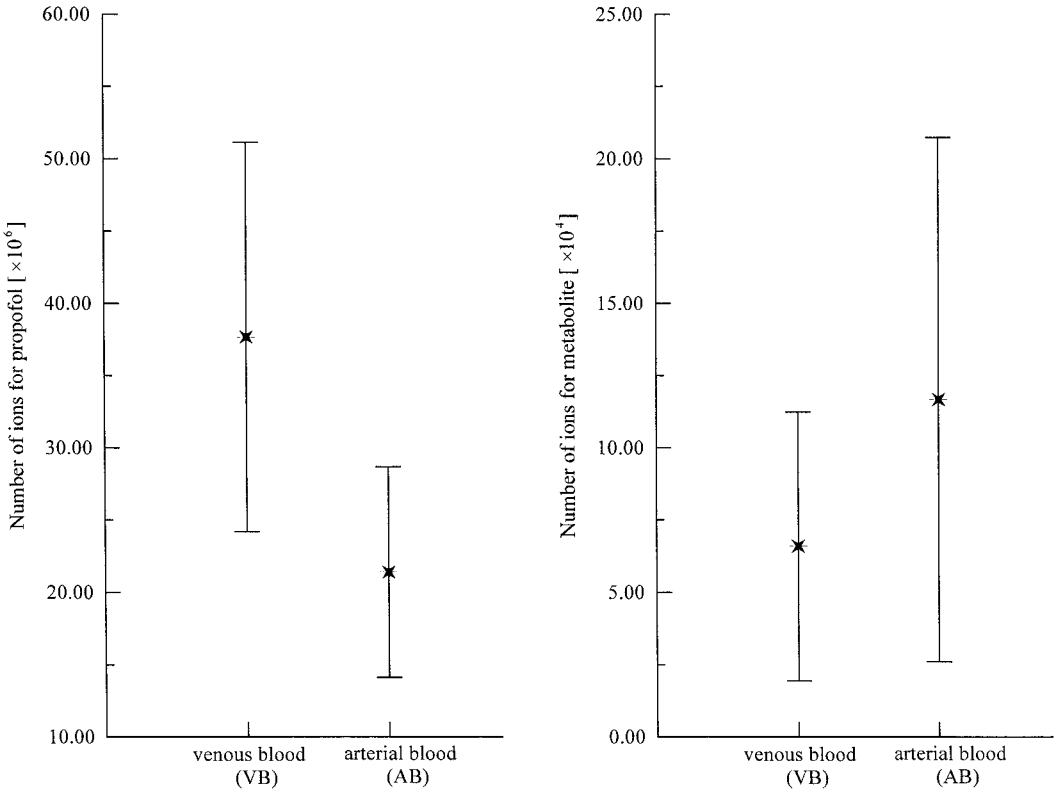

Fig. 3. Total number of ions for propofol and 2,6-diisopropyl-1,4-quinol measured by gas chromatography–mass spectroscopy in blood samples collected from the right atrium (venous blood; C_{VB}) and radial artery (arterial blood; C_{AB}) (n = 11) for group I during infusion.

Discussion

The presented results show that not only the liver but also the lungs are responsible for propofol metabolism in human organism; the decrease of propofol concentrations and the increase of 2,6-diisopropyl-1,4-quinol concentrations in blood after its passage through lungs are observed. As far as the liver is concerned, the clearance of propofol exceeds its capacity in respect of its total blood flow.[1,6,12] Moreover, no significant changes of propofol pharmacokinetics were observed elsewhere in patients with the liver function abnormalities or alterations in the liver blood flow, which suggested the presence of extrahepatic metabolism.[13] At the same time, Mather *et al.*[4] reported a substantial regional propofol blood concentration gradient across lamb's lungs but failed to detect propofol in lung tissues. To explain the role of human lungs in the biotransformation of propofol, first the propofol concentration was examined across human lungs during the drug infusion to determine whether veno-arterial differences occurred. It was found that the concentration of propofol measured by HPLC in group I during infusion of propofol was higher in blood collected from the right atrium than from the radial artery (venous blood and arterial blood in fig. 1); the ratio of drug concentrations for these blood vessels was 1.82 ± 0.39, and the difference was 2.68 ± 1.18 μg/ml (table 1). One possible interpretation of the results is that the observed differences result from the uptake of propofol by tissues or from the drug metabolism. However, a closer consideration of the obtained values indicates these changes can be a result of the dissolution of propofol in blood; the incomplete mixing of propofol in the blood stream was one of the explanations for the influence of sample site on blood concentration of the drug offered by Major *et al.*[14] The collected data were obtained using blood samples taken during the continuous infusion of propofol. Therefore, the diminution of propofol concentration in blood can possibly result from the continuous mixing of propofol with blood during the flow of blood in blood vessels, known as the streaming effect. Moreover, it should also be remembered that the blood from superior vena cava and from inferior vena cava, mixing in the right atrium, can contain various amounts of propofol.

To exclude the possible streaming effect resulting from the continuous propofol infusion, the second series of investigations of propofol concentration in blood was conducted. This time, blood samples for analysis were taken from the same sites as before but 20 min after the termination of propofol infusion. The 20-min period of blood circulation in human organism seems to be sufficiently long to eliminate propofol concentration gradient resulting from the incomplete mixing when propofol was infused, if such effect really existed. The results of

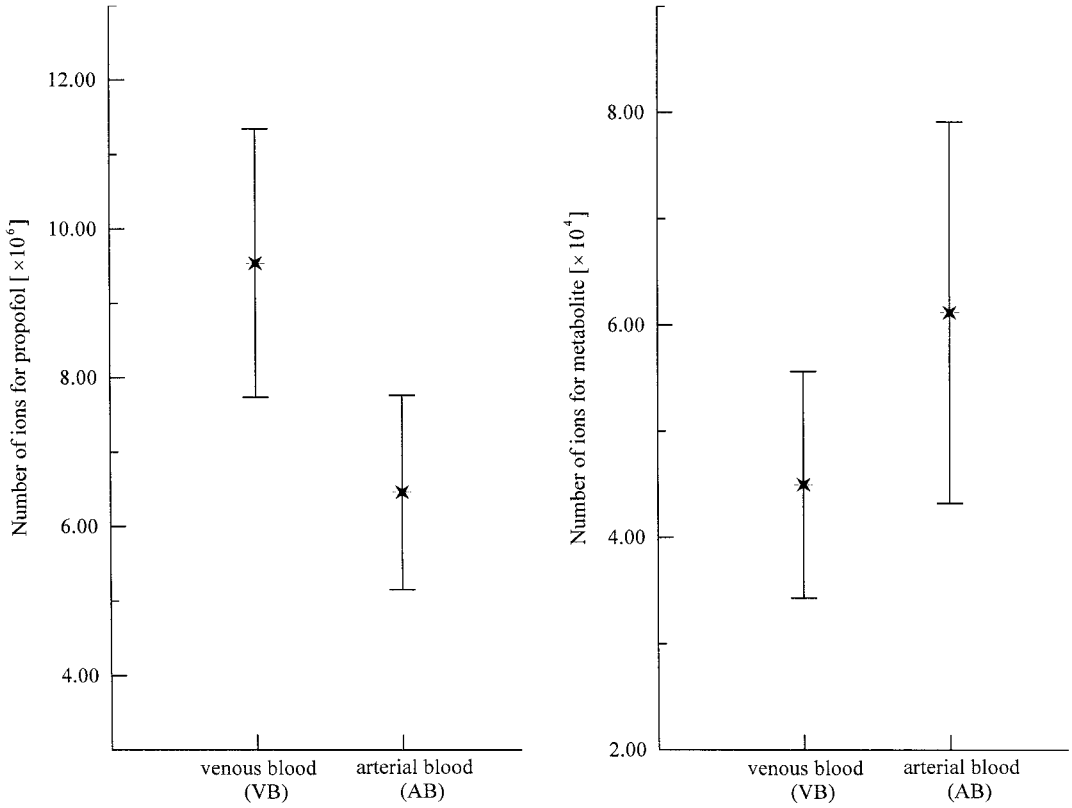

Fig. 4. Total number of ions for propofol and 2,6-diisopropyl-1,4-quinol measured by gas chromatography–mass spectroscopy in blood samples collected from the right atrium (venous blood; C_{VB}) and radial artery (arterial blood; C_{AB}) for group I after termination of infusion (n = 7).

HPLC measurements for group I after termination of propofol infusion (fig. 1) show the same relation for propofol blood concentration as observed during infusion, namely, higher propofol concentration in venous blood and lower in arterial blood; the veno-arterial ratio was 1.58 ± 0.44, and the difference was 0.48 ± 0.33 μg/ml (table 1). Therefore, the decrease of the propofol level was caused by the uptake of propofol, its metabolism, the incomplete mixing effect in the right atrium, or any of these factors operating together.

To further exclude the incomplete mixing effect, blood samples were collected from pulmonary and radial arteries (patients in group II). In group II (fig. 2), higher propofol concentration in blood taken from pulmonary artery (mixed venous blood) than from radial artery (arterial blood) was observed, and the veno-arterial ratio and veno-arterial difference were 1.33 ± 0.35 and 0.97 ± 0.51 μg/ml, respectively. There are many reports showing the essential role of the lungs in the process of drug elimination.[15–17] The data gathered for group II confirm the contribution of the lungs to the process of propofol diminution, which may result from uptake of propofol or its metabolism.

The results discussed thus far are consistent with the aforementioned remarks in the literature and suggest the role of the lungs in propofol clearance.[4,5,18] However, they do not explain the role of the lungs in detail, because the process responsible for the observed differences still remains unknown.

The metabolism of propofol is very rapid.[1–3,12] Approximately half of the drug is excreted in the form of propofol glucuronide conjugates. A significant part of propofol is transformed into 2,6-diisopropyl-1,4-quinol and removed from the organism in the form of sulfate or glucuronide complexes. Only 0.3% of propofol leaves the organism in the unchanged form. The decrease in propofol level in blood after its passing through the lungs observed in group II can be explained by the uptake of the drug by this organ or by the transformation of the drug into one of its metabolites.

Gas chromatography–mass spectroscopy investigations for group I confirmed the presence of 2,6-diisopropyl-1,4-quinol in the blood samples both during and after propofol infusion (figs. 3 and 4). Moreover, the higher level of this metabolite in arterial compared with venous blood was observed (for mean veno-arterial ratio and difference, see table 1). The increase of 2,6-diisopropyl-1,4-quinol concentration in blood after its passage through the lungs and the simultaneous decrease of propofol concentration (figs. 3 and 4) suggest that a part of the drug is transformed by the lungs into a quinol derivate. In addition, during total intravenous anesthesia, the mean ratio of propofol amount in venous blood to that in arterial blood is almost the same as the mean ratio

of 2,6-diisopropyl-1,4-quinol amount in artery blood to that in venous blood (1.77 ± 0.37 and 1.81 ± 0.59, $P = 0.99$) and nearing the ratio from HPLC measurements (1.82 ± 0.39). The same conclusion can be offered considering the analogous ratios after total intravenous anesthesia: 1.50 ± 0.25, 1.36 ± 0.22 ($P = 0.176$), and 1.58 ± 0.44. The similarities of the ratios for propofol support the validity and reliability of the obtained data, and the similarities of the ratios for propofol and its quinol derivate further prove that the lungs metabolize propofol.

All of the aforementioned observations indicate that the lungs are as much involved in the transformation of propofol as the liver. Of course, the transformation of propofol into 2,6-diisopropyl-1,4-quinol may not be the only process that the drug undergoes in the lungs. Veroli *at al.*[5] showed the presence of propofol glucuronide complex in human organism at the absence of the liver, whereas Matot at al.[18] reported the ability of cats' lungs to take up propofol. Therefore, partial uptake of propofol by human lungs or a formation of the other mentioned metabolites in the lungs are also possible. Further investigations are required to describe in detail the role of the lungs in the process of clearing human organism of propofol.

References

1. Langley MS, Heel RC: Propofol: A review of its pharmacodynamic and pharmacokinetic properties and use as an intravenous anaesthetic. Drugs 1988; 35:334–72

2. Kanto J, Gepts E: Pharmacokinetic implications for the clinical use of propofol. Clin Pharmacokinet 1989; 17:308–26

3. Kanto JH: Propofol, the newest induction agent of anesthesia. Int J Clin Pharmacol Ther Toxic 1988; 26:41–57

4. Mather LE, Selby DG, Runciman WB, McLean CF: Propofol, assay and regional mass balance in the sheep. Xenobiotica 1989; 19:1337–47

5. Veroli P, O'Kelly B, Bertrand F, Trouvin JH, Farinotti R, Ecoffey C: Extrahepatic metabolism of propofol in man during the anhepatic phase of orthotopic liver transplantation. Br J Anaesth 1992; 68:183–6

6. Cockshott ID, Briggs LP, Douglas EJ, White M: Pharmacokinetics of propofol in female patients: Studies using single bolus injections. Br J Anaesth 1987; 59:1103–10

7. Lange H, Stephan H, Rieke H, Kellermann M, Sonntag H, Bircher J: Hepatic and extrahepatic disposition of propofol in patients undergoing coronary bypass surgery. Br J Anaesth 1990; 64:563–70

8. Le Guellec C, Lacarelle B, Villard PH, Point H, Catalin J, Durand A: Glucuronidation of propofol in microsomal fractions from various tissues and species including humans: Effect of different drugs. Anesth Analg 1995; 81:855–61

9. Gray PA, Park GR, Cockshott ID, Douglas EJ, Shuker B, Simons PJ: Propofol metabolism in man during the anhepatic and reperfusion phases of liver transplantation. Xenobiotica 1992; 22:105–14

10. de Grood PM, Mitsukuri S, van Egmond J, Rutten JM, Crul JF: Comparison of etomidate and propofol for anaesthesia in microlaryngeal surgery. Anaesthesia 1987; 42:366–72

11. de Grood PM, Harbers JB, van Egmond J, Crul JF: Anaesthesia for laparoscopy: A comparison of five techniques including propofol, etomidate, thiopentane and isoflurane. Anaesthesia 1987; 42:815–23

12. Simons PJ, Cockshott D, Douglas EJ, Gordon EA, Hopkins K, Rowland M: Disposition in male volunteers of subanaesthetic intravenous dose of an oil in water emulsion of 14C-propofol. Xenobiotica 1988; 18:429–40

13. Shafer A, Doze VA, Shafer SL, White PF: Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia. ANESTHESIOLOGY 1988; 69:348–56

14. Major E, Aun C, Yate PM, Savege TM, Verniquet AJ, Adam H, Douglas EJ: Influence of sample site on blood concentrations of ICI 35 868. Br J Anaesth 1983; 55:371–5

15. Nyberg SL, Mann HJ, Hu MY, Payne WD, Hu WS, Cerra FB, Remmel RP: Extrahepatic metabolism of 4-methylumbelliferone and lidocaine in the anhepatic rabbit. Drug Metab Dispos 1996; 24:643–8

16. Park GR, Manara AR, Dawling S: Extra-hepatic metabolism of midazolam. Br J Clin Pharmacol 1989; 27:634–7

17. Krishna DR, Klotz U: Extrahepatic metabolism of drugs in humans. Clin Pharmacokinet 1994; 26:144–60

18. Matot I, Neely CF, Katz RY, Neufeld GR: Pulmonary uptake of propofol in cats: Effect of fentanyl and halothane. ANESTHESIOLOGY 1993; 78:1157–65