PULMONARY METABOLISM OF PROPOFOL DURING ANHEPATIC PHASE OF ORTHOTOPIC LIVER TRANSPLANTATION IN PIGS

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ABSTRACT

Objective: Propofol is a widely used intravenous anesthetic agent which has a total body clearance exceeding hepatic blood flow which suggests extrahepatic metabolism. We therefore assessed the pulmonary metabolism of propofol during the anhepatic phase of orthotopic liver transplantation in pigs.

Methods: Seven adult female pigs weighing 30.0±3.37 kg during anhepatic phase of orthotopic liver transplantation were studied. Intravenous anesthesia was induced with 3.5 mg/kg propofol and after endotracheal intubation, anesthesia was maintained with 15 mg/kg/h propofol and 1 µg/kg/min alfentanil infusion following a 10 µg/kg alfentanil bolus. Propofol concentrations from the pulmonary and carotid artery and propofol metabolites in the urine were measured by capillary gas chromatography before the anhepatic phase, every 15 minute during the anhepatic phase and at 30 minute intervals during reperfusion.

Results: During the anhepatic phase, propofol concentrations in the pulmonary and carotid artery increased significantly ($p<0.05$) but propofol metabolites in urine did not change ($p>0.05$). Although propofol concentration in the pulmonary artery was higher than that of the carotid artery, the difference was not statistically significant. The mean extraction coefficient was 0.13.

Conclusion: We conclude that propofol has low pulmonary extraction and other organs or tissues, such as gut wall, may be responsible for the extrahepatic metabolism of propofol.

Key Words: Anesthetics, intravenous; propofol
Biotransformation; extrahepatic metabolism
Surgery, orthotopic liver transplantation

INTRODUCTION

Propofol (2,6-diisopropylphenol) has become increasingly popular as an intravenous anesthetic for induction and maintenance of general anesthesia, as well as for sedation during regional anesthesia and in critically ill patients because of the anesthesia quality and rate of recovery and good control of anesthetic depth whether it is given by bolus or continuous infusion (1-4). The short duration of action of propofol was explained by the high total body clearance exceeding the capacity of the liver blood flow suggesting that extrahepatic mechanisms contribute to the clearance of propofol. However conflicting results about the extrahepatic metabolism of propofol were published (5-17). Therefore we aimed to investigate pulmonary metabolism of propofol in pigs during the anhepatic phase of orthotopic liver transplantation which provides a unique opportunity to evaluate the extrahepatic metabolism of drugs.

MATERIALS AND METHODS

After Institutional Ethical Committee approval, 7 adult female pigs weighing 30.0±3.37 kg and undergoing orthotopic liver transplantation were included in the study protocol. Pigs were premedicated with 10mg/kg ketamine intraperitoneally 30 minutes before anesthesia. Anesthesia was induced with 3.5 mg/kg propofol i.v. and pigs were intubated endotracheally. After administration of 10µg/kg alfentanil bolus, anesthesia was maintained with 15 mg/kg/h propofol and 1 µg/kg/min alfentanil infusions. 0.1 mg/kg pancuronium bromide i.v. was given for neuromuscular blockade. The lungs were ventilated with 100% oxygen to maintain normocapnia as verified by arterial blood gas analysis and carbondioxide concentration in end expired gas was determined by capnography.

The right carotid artery was cannulated for mean arterial pressure measurement. A 7-French gauge triple lumen pulmonary arterial thermodilution catheter was inserted via the left jugular vein and the wedge position was verified by the pressure curve. The right jugular vein was also used for venovenous bypass. Heart rate, mean arterial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, oxygen saturation and end tidal carbondioxide were measured with Protocol Propaq 106 EL monitor. Arterial blood gas measurement, hematocrit and electrolyte values were obtained from Mallinckrodt Gem Stat blood gas analyser. A 14 French Foley catheter was inserted to collect urine samples.

Blood samples were obtained from the right external carotid and pulmonary artery and collected in plastic tubes containing potassium oxalat anticoagulant. Blood samples were immediately centrifuged and plasma was frozen at -20 °C before propofol concentration analysis with capillary gas chromatography (18). Urine samples were also frozen at -20°C until measuring the propofol metabolites by capillary gas chromatography.

Laboratory analysis of plasma propofol concentration and propofol metabolites in urine: Pure propofol standard (Propofol -diisoprofol-2,6- diisopropylphenol, Zeneca) and 50 µl 1 M sodium hydoxide for alkalinization were added to control pig plasma not containing propofol. After shaking on a vortex mixer for 5 minutes with 500 µl of chloroform as an internal standard, it was centrifuged at 15000 rpm for 4 minutes and a 300-µl portion of the chloroform layer was placed in ependorph tube and filled with nitrogen gas to protect from oxidation. The solution was again vortexed with 50 µl chloroform and the chloroform layer was analysed by gas chromatography (HNU Systems GC 421 FID detector. Colon: NBW-351 Nitroterephalate modified polyethylene glycol). The same technique was applied to pig plasma containing propofol. For measurement of propofol metabolites in urine; 1 ml of phosphate buffer and 100 µl beta-glucuronidase (2000 U/ml) solution were added to 1 ml of urine. The mixture was incubated at 25°C for 48 hours and extracted with 1 ml chloroform. Extract was evaporated to dryness and redissolved with 50 µl chloroform. 1 µl of this solution was injected to gas chromatography.

All hemodynamic parameters were recorded and blood and urine samples were collected one hour after infusion (before the anhepatic phase) at 15 minute intervals during the anhepatic phase and every 30 minute during the reperfusion phase. The results were analysed statistically using nonparametric Friedman, Wilcoxon Matched Pairs test and Dunn's multiple comparison test and a $p<0.05$ was accepted as statistically significant.

Extraction coefficient was calculated by (pulmonary artery concentration-carotid artery concentration) / pulmonary artery concentration (13).

RESULTS

The duration of anesthesia and anhepatic phase and total doses of propofol and alfentanil were shown in Table I.

At 15th minute of anhepatic phase mean arterial pressure and pulmonary capillary pressure decreased and heart rate increased significantly ($p<0.05$) (Table II). During reperfusion phase, while heart rate decreased and pulmonary capillary pressure increased, mean arterial pressure remained decreased.

During anesthesia PaO2 and PaCO2 remained stable but pH decreased significantly at 15^{th} minute of anhepatic phase ($p<0.05$).

In all pigs propofol concentration in pulmonary and carotid artery increased significantly during 30^{th} minute of anhepatic phase and returned to preanhepatic values during reperfusion phase ($p<0.05$) (Table II). During anhepatic phase in 4 of 7 pigs, propofol concentration of pulmonary artery was higher than that of carotid artery but the difference of the mean concentrations of 7 pigs was not statistically significant ($p>0.05$). The mean extraction coefficient was calculated as 0.13.

No statistically significant difference was observed between the propofol metabolites in urine during preanhepatic and anhepatic phase ($p>0.05$) (Table III). Also unchanged propofol was not detected in the urine.

Table I. The duration of anesthesia, anhepatic phase and total doses of propofol and alfentanil (Mean±SD)

Duration of anesthesia	(min)	210.0±41.43
Duration of anhepatic phase	(min)	56.57±10.59
Total dose of propofol	(mg)	1375.14±55.96
Total dose of alfentanil	(µg)	7191.00±25.67

Table II. The plasma propofol concentration of pulmonary artery and carotid artery (µg/ml) (Mean±SD)

	Pulmonary artery	Carotid artery
First hour	7.88±6.06	5.78±3.05
Preanhepatic phase	6.62±6.14	7.95±3.68
Anhepatic 15.min	10.14±6.53*	10.00±5.24*
Anhepatic 30.min	15.22±16.1*	10.58±5.57*
Anhepatic 45.min	12.20±7.78*	10.45±5.16*
Reperfusion 30.min	7.10±4.08	7.17±3.61
Reperfusion 60.min	9.32±5.51	9.88±6.60

*p<0.05

Table III. The metabolites of propofol in the urine (µg/ml)

	Preanhepatic phase	Anhepatic 30.min	Anhepatic 45.min
1.pig	1.18	1.15	0.87
2.pig	2.57	3.06	1.55
3.pig	1.37	1.02	2.11
4.pig	1.41	2.26	4.53
5.pig	1.08	2.03	2.72
6.pig	2.99	2.57	2.67
7.pig	0.99	2.34	1.05
Mean	1.65±0.79	2.06±0.74	2.21±1.25

DISCUSSION

Propofol having a high total clearance exceeding the capacity of the liver blood flow is widely accepted to be among the drugs having extrahepatic metabolism such as morphine and midazolam (1-17). Studies in rats with phenolic substrates which are metabolized mainly by direct conjugation indicate that lung, intestinal wall and kidney are major extrahepatic sites of conjugation (19). These organs receive either all or a large proportion of cardiac output. Thus even if such organs show a low extraction ratio of propofol from blood they could make a measurable contribution to its total body clearance (13, 14, 16). In humans propofol is known to be metabolized by direct conjugation of the phenolic hydroxyl group and by sulphate and glucuronic acid conjugation of 2, 3-diisopropyl - 1,4-quinol derivative (1-4).

Up to date all studies about the extrahepatic metabolism of propofol are focused on pulmonary metabolism as lungs are known to be able to conjugate phenol over a wider dose range than liver and receive a significant proportion of the total cardiac output. However conflicting results about pulmonary metabolism of propofol have been published (13-16). Servin and colleagues (13) showed that isolated, ventilated and perfused rat lungs were able to trap and conjugate propofol with a low extraction coefficient (E=0.1). Mather and

colleagues (14) studied regional kinetics and mass balance of propofol administered i.v. as a bolus or as an infusion in sheep. Substantial regional blood concentration gradients were observed across the lungs and the liver indicated a high clearance or extensive uptake of propofol into lungs and hepatosplanchnic system. The fact that the pulmonary uptake was caused more by clearance than by distribution was supported by their failure to detect propofol in lung tissue. However Lange and colleagues (15) determined a smaller area under curve (AUC) by pulmonary arterial samples compared with the AUC from systemic arterial samples with a single intravenous bolus dose of propofol 2 mg/kg for induction of anesthesia in patients undergoing coronary bypass surgery and did not suggest pulmonary removal of propofol in man. Gray and colleagues (16) in their study with radiolabelled propofol during liver transplantation in man concluded that extrahepatic metabolism of propofol was evident in all patients but there was no evidence the lungs contributed to the metabolism of propofol. These conflicted results constitude the aim of our study.

Orthotopic liver transplantation provides a unique opportunity to study the extrahepatic metabolism of drugs. During the anhepatic period when the patient has no perfused liver, extrahepatic sites of drug metabolism can be sought in the absence of the large hepatic component of metabolism which would usually make the identification of extrahepatic metabolism impossible (16,17). Besides, the comparison of the level of metabolites during preanhepatic and anhepatic phases provides an opportunity to determine the effectiveness of extrahepatic metabolism.

In our study; during anhepatic phase the difference of propofol concentrations between pulmonary and carotid artery in 4 of 7 pigs and the presence of propofol metabolites in the urine confirm the pulmonary metabolism of propofol with a low extraction coefficient. According to Mather and colleagues (14), because of the large pulmonary blood flow the pulmonary extraction ratio needs only to be small to account for appreciable clearance. Servin and colleagues (13) also found the pulmonary extraction coefficient as low as 0.1. We thought that interpatient variability reflecting genetic differences in isozyme activity, analytic errors and the unpredictable differences in organ functions could be responsible for the results of other 3 pigs. Howéver in 7 pigs, the mean propofol concentration of pulmonary artery was higher than that of carotid artery also, but the differences was not statistically significant.

The significant increase in pulmonary artery and carotid artery concentrations of propofol during anhepatic phase can be explained by low enzyme capacity of lungs and by cross clamping of the hepatic vessels and the inferior vena cava with subsequent diminution in cardiac index after a reduced venous return and tissue hypoperfusion. As propofol metabolites in the urine remained unchanged while the plasma concentrations of propofol increased significantly during the anhepatic phase, we conclude that other organs and tissues having conjugation capacity such as intestinal wall can also contribute to the extrahepatic metabolism of propofol.

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