Laboratory Investigations

The influence of hypoxia and hyperoxia on the kinetics of propofol emulsion

Ken Yamamoto MD,
Tsunehisa Tsubokawa MD,
Toshihiro Yagi MD,
Shuichi Ishizuka MD,
Shigeo Ohmura MD,
Tsutomu Kobayashi MD

Purpose: To study the effect of hypoxia and hyperoxia on the pharmacokinetics of propofol emulsion, hepatic blood flow and arterial ketone body ratio in the rabbit.

Methods: Twenty four male rabbits were anesthetized with isoflurane (1.5-2 %) in oxygen. After the surgical procedure, isoflurane administration was discontinued and intravenous propofol infusion (30 mg·kg⁻¹·hr⁻¹) was started. The infusion rate of propofol was maintained throughout the study. After an initial 90 min period of propofol infusion, rabbits were randomly allocated to one of three groups: hypoxia (F_IO₂ = 0.1), normoxia (F_IO₂ = 0.21), and hyperoxia (F_IO₂ = 1.0). Propofol infusion was continued under the allocated F_IO₂ for 60 min. Propofol concentrations in arterial blood, total body clearance of propofol, hepatic blood flow and arterial ketone body ratio were measured.

Results: The mean arterial propofol concentration at the end of infusion was higher in the hypoxia group (15.2 ± 2.8 µg·mL⁻¹, mean ± SD) than in the normoxia (7.4 ± 1.7) and hyperoxia (8.0 ± 1.9) groups (*P* < 0.05). Total body clearance of propofol, hepatic blood flow and arterial ketone body ratio were all reduced in the hypoxia group (*P* < 0.05). Total ketone body concentration in arterial blood increased in the hyperoxia group (*P* < 0.01).

Conclusion: Hypoxia produced an accumulation of propofol in blood and reduced propofol clearance. These changes could result from decreased hepatic blood flow and low cellular energy charge in the liver. Hyperoxia, on the other hand, increased total ketone body in arterial blood.

Objectif : Étudier l'effet de l'hypoxie et de l'hyperoxie sur la pharmacocinétique de l'émulsion de propofol et le ratio débit sanguin hépatique-corps cétoniques artériels chez le lapin.

Méthode : Vingt-quatre lapins mâles ont été anesthésiés avec un mélange de sévoflurane (1,5-2 %) et d'oxygène. Après l'opération, on a stoppé l'administration d'isoflurane et commencé la perfusion intraveineuse de propofol (30 mg·kg⁻¹·hr⁻¹). La vitesse de perfusion du propofol a été maintenue tout au long de l'étude. À la suite d'une perfusion initiale de propofol de 90 min, les lapins ont été répartis au hasard en trois groupes : hypoxie (F_IO₂ = 0,1), normoxie (F_IO₂ = 0,21) et hyperoxie (F_IO₂ = 1,0). La perfusion de propofol s'est poursuivie pendant 60 min quelle que soit la F_IO₂ choisie. On a mesuré : les concentrations de propofol dans le sang artériel, la clairance corporelle totale du propofol, le ratio débit sanguin hépatique-corps cétoniques artériels.

Résultats : La concentration artérielle moyenne de propofol, à la fin de la perfusion, était plus élevée dans le groupe hypoxie (15,2 ± 2,8 µg·mL⁻¹, moyenne ± écart type) que dans le groupe normoxie (7,4 ± 1,7) et hyperoxie (8,0 ± 1,9) (*P* < 0,05). La clairance corporelle totale du propofol, le ratio débit sanguin hépatique-corps cétoniques artériels ont tous été réduits dans le groupe hypoxie (*P* < 0,05). La concentration corporelle totale de cétone dans le sang artériel était plus élevée dans le groupe hyperoxie (*P* < 0,01).

Conclusion : L'hypoxie a provoqué une accumulation de propofol dans le sang et a réduit la clairance du propofol. Ces changements peuvent résulter d'une réduction du débit sanguin hépatique et d'une faible charge énergétique cellulaire hépatique. Par ailleurs, l'hyperoxie augmente la concentration totale des corps cétoniques artériels.

From the Department of Anesthesiology and Intensive Care Medicine, School of Medicine, Kanazawa University, Kanazawa, Japan.

Address correspondence to: Ken Yamamoto MD, Department of Anesthesiology and Intensive Care Medicine, School of Medicine, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8641, Japan. Phone: +81-76-265-2431; Fax: +81-76-234-4267;

E-mail: kenyam@med.kanazawa-u.ac.jp

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IN the critical care setting propofol (Diprivan™, Zeneca Pharmaceuticals, Osaka, Japan) is used to sedate and anesthetize patients who are hypoxic from lung disease, or who are maintained in a hyperoxic state to meet a therapeutic goal (e.g. treatment of anerobic infection). Although the rapid decline of propofol concentrations in arterial blood after the termination of infusion and its high hepatic clearance have been recognized,¹ there are few reports on the influence of hypoxia and hyperoxia on the kinetics of propofol emulsion. In addition, propofol emulsion might be a cause of ketonuria² and metabolic acidosis.³⁻⁵ Therefore, we studied the effects of arterial oxygen partial pressure on the pharmacokinetics of propofol emulsion, organ blood flow and arterial ketone body ratio in the rabbit.

Methods

Study design

Following approval of the study protocol by the Animal Investigation Committee of our institute, 24 male Japanese rabbits (3.1-3.7 kg in body weight) were studied. Rabbits were fed laboratory chow and drank water *ad libitum* for at least one week before the experiment. Anesthesia was induced with isoflurane (1.5-2 %) in oxygen and a 24G indwelling intravenous catheter was inserted into the ear vein. Lactated Ringer's solution (10 mL·kg⁻¹·hr⁻¹) was infused via the catheter throughout the experiment. Rabbits were placed on a surgical board equipped with a heating lamp to maintain body temperature and mechanically ventilated with a ventilator for small animals (SN-480-5, Shinano, Tokyo, Japan) via a tracheotomy. Muscle relaxation was provided using pancuronium and a lead II electrocardiogram was used to record the heart rate. Tidal volume, respiratory rate and positive end-expiratory pressure were kept at 15 mL·kg⁻¹, 30 bpm and 2.0 cm H₂O, respectively. Two indwelling catheters (18G, 44 mm) were inserted into the right femoral artery and external jugular vein. These catheters were connected to transducers (2G82, Nihon Denki San-ei, Tokyo, Japan) to monitor arterial and central venous pressures continuously. Arterial blood gas analysis was performed using an automatic blood gas analyzer (ABL-3, Radiometer, Copenhagen, Denmark). Organ blood flow and cardiac output were measured using a coloured microsphere technique. An epidural catheter (30 cm long, 1.0 mm diameter) was inserted through the right common carotid artery into the left ventricle. Coloured polystyrene microspheres of 15 µm in diameter (E-Z Tract, Los Angeles, CA, USA) were injected through the catheter to measure the organ blood flow.

After the surgical procedure, respiratory rate was adjusted to keep PaCO₂ at 30-35 mmHg and ventila-

tor settings were then held constant throughout the experiment. Initial arterial blood samples (2.0 mL) were obtained to determine control values for blood gases and arterial ketone body ratios. Isoflurane administration was then discontinued and propofol (Diprivan™, Zeneca Pharmaceuticals, Osaka, Japan) infusion (30 mg·kg⁻¹·hr⁻¹) was started. This infusion rate of propofol was maintained for 150 min until the end of experiment. Propofol infusion was continued under mechanical ventilation with oxygen, 100% inspired, for 90 min. The animals were then randomly allocated to one of three groups with different inspired oxygen concentrations: hypoxia (F_IO₂ = 0.1), normoxia (F_IO₂ = 0.21), and hyperoxia (F_IO₂ = 1.0). Propofol concentrations in arterial blood were measured at 0, 30 and 60 min (C_{ss}) after the allocation. Five million particles of coloured microspheres were injected into the left ventricle through the catheter at 60 min after the allocation. Arterial blood was drained from the femoral artery at a constant rate of 5.0 mL·min⁻¹ for one minute to calculate cardiac output. Total body clearance (CL_T) of propofol was calculated as infusion rate·C_{ss}⁻¹. Then, propofol infusion was stopped and arterial blood samples were obtained every two minutes for 10 min after the termination of propofol infusion. At the end of the experiment, the animals were sacrificed with propofol and KCl *iv*. The fractional organ blood flows in the liver, stomach, intestine, omentum, spleen, and pancreas were calculated by counting the number of coloured microspheres extracted from each organ.⁶ The hepatic artery blood flow (HAF) was calculated from the microsphere count in the liver. Portal vein blood flow (PVF) was estimated to be the sum of blood flow to the stomach, intestine, omentum, spleen and pancreas. Total hepatic blood flow (THBF) was defined as a sum of HAF and PVF. Hepatic extraction ratio of propofol (E_H) was calculated as CL_T/THBF.

Measurement of propofol concentration, total ketone body concentration and arterial ketone body ratio

Propofol concentration in whole blood was measured with high performance liquid chromatography and fluorescence detection.⁷ The minimum detectable concentration of propofol in whole blood was 0.5 µg·mL⁻¹ with coefficient of variation of 7%. A calibration curve was made for each rabbit using its own arterial blood obtained before propofol infusion. The sum of acetoacetate and 3-hydroxybutyrate concentrations (total ketone body concentration, TKB), as well as the ratio of acetoacetate:3-hydroxybutyrate in arterial blood (arterial ketone body ratio, AKBR) were measured to estimate hepatic mitochondrial redox potential. The AKBR

FIGURE 1 Propofol concentrations in arterial blood with three inspired oxygen concentrations. The mean blood concentration of propofol showed more than two-fold increase in the hypoxia group (open square, $n=8$) compared with normoxia (open circle, $n=8$) and hyperoxia (closed circle, $n=8$) groups at the end of propofol infusion.

* $P < 0.05$ compared with the contemporary data of normoxia and hyperoxia groups.

† $P < 0.01$ compared with the allocation point.

Values are mean $\pm$ SD. Some SD bars are omitted for clarity.

reflects the free NAD^+/NADH ratio in the mitochondria and, hence, is a useful parameter in assessing the cellular energy charge levels in hepatocytes.⁸⁻¹⁰ A commercially available ketone body analyzer (Ketorex™, Sanwa Kagaku Co. Ltd., Nagoya, Japan) and a semiautomatic spectrophotometer (KETO 340™, Ihara Electric Co. Ltd., Kasugai, Japan) were used for the measurement of TKB and AKBR.

Statistical Analysis

All data are expressed as mean $\pm$ SD. Differences among multiple group means were made using one-way analysis of variance. Arterial propofol concentrations were compared using two-way analysis of variance with repeated measures. Multiple comparisons were carried out with Tukey test. Differences between groups were considered significant at $P < 0.05$. Statistical analysis was performed using SigmaStat™ ver 2.0 for Windows (Jandel Corporation, San Rafael, CA, USA).

Results

There were no differences among groups for body weight, or control values of blood pressure, heart rate, blood gas values, arterial ketone body concentrations or ketone body ratios. Total dose of propofol (75

FIGURE 2 Individual propofol concentration-time data with three inspired oxygen concentrations. A: hypoxia group ($n=8$). B: normoxia group ($n=8$). C: hyperoxia group ($n=8$).

$\text{mg}\cdot\text{kg}^{-1}$) and lipid ($750 \text{ mg}\cdot\text{kg}^{-1}$) contained in propofol preparations were identical in all animals.

Propofol concentrations in arterial blood in hypoxia, normoxia and hyperoxia groups at the allocation were 7.1 ± 3.0 , 6.4 ± 2.2 , and $7.3 \pm 2.1 \text{ }\mu\text{g}\cdot\text{mL}^{-1}$, respectively ($P = 0.77$). Propofol concentrations at the end of infusion in the normoxia (7.4 ± 1.7) and hyperoxia (8.0 ± 1.9) groups did not change from the allocation point. On the other hand, propofol concentrations at the end

TABLE I Physiological values at the end of propofol infusion

Group	<i>n</i>	HR (bpm)	BP (mmHg)	pH	PaCO ₂ (mmHg)	PaO ₂ (mmHg)
Hypoxia	8	209 ± 30*	89 ± 10*†	7.21 ± 0.08*†	30.7 ± 4.6*	44.2 ± 4.0*†
Normoxia	8	257 ± 24	111 ± 9	7.38 ± 0.07	38.2 ± 3.6	107.6 ± 21.1
Hyperoxia	8	237 ± 38	110 ± 9	7.41 ± 0.05	30.4 ± 4.3*	596.6 ± 55.7*

**P* < 0.05 *vs* normoxia, †*P* < 0.05 *vs* hyperoxia

Values are mean ± SD

HR: heart rate, BP: systolic blood pressure

TABLE II Cardiac output and hepatic blood flow at the end of propofol infusion

Group	<i>n</i>	CO (mL·min ⁻¹ ·kg ⁻¹)	HAF (mL·min ⁻¹ ·kg ⁻¹)	PVF (mL·min ⁻¹ ·kg ⁻¹)	THBF (mL·min ⁻¹ ·kg ⁻¹)
Hypoxia	8	191 ± 25*†	8.1 ± 4.1*	52.9 ± 11.6	61.4 ± 12.2*
Normoxia	8	238 ± 23	18.3 ± 10.1	65.0 ± 9.4	83.4 ± 14.1
Hyperoxia	8	230 ± 26	13.3 ± 5.2	64.1 ± 12.4	73.4 ± 12.3

**P* < 0.05 *vs* normoxia, †*P* < 0.05 *vs* hyperoxia

Values are mean ± SD

CO: cardiac output, HAF: hepatic artery blood flow, PVF: portal vein blood flow, THBF: total hepatic blood flow

TABLE III Total body clearance and hepatic extraction ratio under different F_IO₂

Group	<i>n</i>	CL _T (mL·min ⁻¹ ·kg ⁻¹)	E _H
Hypoxia	8	33.8 ± 6.0*†	0.57 ± 0.17*†
Normoxia	8	70.5 ± 16.5	0.85 ± 0.19
Hyperoxia	8	65.3 ± 14.6	0.89 ± 0.18

**P* < 0.01 *vs* normoxia, †*P* < 0.01 *vs* hyperoxia

Values are mean ± SD

CL_T: total body clearance, E_H: hepatic extraction ratio

TABLE IV Arterial ketone body ratio and total ketone body concentration before and at the end of propofol infusion

Group	<i>n</i>	AKBR		TKB (μM·L ⁻¹)	
		Before Infusion	End Infusion	Before Infusion	End Infusion
Hypoxia	8	0.78 ± 0.30	0.16 ± 0.10*†	94 ± 33	128 ± 42
Normoxia	8	0.62 ± 0.24	0.66 ± 0.17	126 ± 42	201 ± 49
Hyperoxia	8	0.76 ± 0.23	0.53 ± 0.09	133 ± 56	556 ± 161*†

**P* < 0.01 *vs* normoxia, †*P* < 0.01 *vs* hyperoxia, ‡*P* < 0.01 *vs* hypoxia

Values are mean ± SD

AKBR: arterial ketone body ratio, TKB: total ketone body concentration

of the propofol infusion in the hypoxia group increased to 15.2 ± 2.8 μg·mL⁻¹. The mean blood concentration of propofol showed a more than two-fold increase in the hypoxia group (*P* < 0.05 *vs* normoxia and hyperox-

ia groups, *P* < 0.01 *vs* the allocation point) (Figure 1). Figure 2 shows individual concentration-time data in three groups. Three of eight rabbits in the hypoxia group attained plateau concentrations at 60 min (Figure 2).

The mean systolic blood pressure and arterial pH decreased in the hypoxia group compared with the other two groups by the end of the infusion (Table I). Cardiac output, HAF and THBF also decreased in the hypoxia group (Table II). In consequence, CL_T and E_H were depressed in the hypoxia group (*P* < 0.01) (Table III).

The arterial ketone body ratio was decreased in the hypoxia group (*P* < 0.01), while the TKB showed an increase in the hyperoxia group (*P* < 0.01) when compared with the other groups (Table IV).

Discussion

Hypoxia resulted in elevated arterial propofol concentrations and a delayed propofol clearance. These changes could result from decreased hepatic blood flow and/or a decreased hepatic extraction ratio of propofol. Drugs with clearance that approaches hepatic blood flow, such as propofol, will be flow-limited drugs, and thus the clearance would be expected to change proportionally with liver blood flow. In part, this explains the reduced clearance in the hypoxia group. Because of the multiple blood sampling in our experiment, we could not measure blood propofol concentrations for long enough to estimate the elimination phase.

Therefore, we used clearance as a model-independent pharmacokinetic parameter to compare the groups. The terminal elimination half-life of propofol in the rabbit is reported to be 16¹¹ and 17 min.¹² We selected 90 min infusion of propofol before the allocation to ensure more than five elimination half-lives. On the other hand, the 60 min infusion of propofol in the hypoxic state might have underestimated steady-state propofol concentrations and overestimated total body clearance. Some animals in the hypoxia group may have attained higher plateau concentrations of propofol as the infusion continued. Total body clearance of propofol in the hypoxia group would be further suppressed with the higher steady-state concentration of propofol.

Hypoxia increases hepatic blood flow¹³ and cardiac output¹⁴ while anesthetic agent added to hypoxic rats suppresses hepatic blood flow and cardiac output.¹⁵ The cause of the reduced hepatic blood flow in the present study is unclear, but reduced cardiac output, hepatic parenchymal hypoxia, and the direct effects of propofol on liver blood flow^{16,17} may all have had a role.

The liver is the major organ for propofol metabolism, with a high hepatic extraction ratio (0.87(ewes)¹⁸ and 0.82 (humans)¹⁹), although propofol is known to be metabolized extrahepatically to some extent.²⁰⁻²³ The principal metabolites of propofol in human volunteers are propofol glucuronide conjugates (40%), glucuronide and sulphate conjugates of its hydroxylated derivative (60%).²⁴ Hydroxylation (phase I reactions) is mediated by the cytochrome P-450 while cytosolic transferases catalyze conjugation (phase II reactions). The hallmark of phase II conjugation reactions is their requirement for energy. Hypoxia is known to reduce the activity of hepatic biotransformation because of a decrease in selected isoenzymes of the hepatic cytochrome P-450.²² Jordi-Racine *et al.*²⁵ report that hepatic P-450 content may reduce after exposure to hypoxia ($F_{I}O_2 = 0.07$) for one hour in rats. Glucuronide conjugation reactions are also suppressed by hypoxia in mice.²⁶

The reduced hepatic extraction ratio observed in the hypoxia group may reflect delayed uptake and metabolism of propofol by the hepatocytes. The change in the arterial ketone body ratio supports this assumption because it is a parameter which reflects the $NAD^+/NADH$ ratio and thus the redox state of liver mitochondria. Low arterial ketone body ratio denotes low cellular energy charge in the liver.⁸⁻¹⁰ Decreased arterial ketone body ratio secondary to hypoxia could be the cause of reduced hepatic extraction ratio and impaired metabolic processes, especially conjugation reactions which require cellular energy.

Contrary to the hypoxia group, total ketone body concentration increased in hyperoxia group under

mechanical ventilation with oxygen 100%. While the relationship between propofol infusion and the development of metabolic acidosis is controversial,^{2-5,27} altered fat metabolism could produce ketoacidosis with prolonged or high-dose propofol administration. Free fatty acids derived from the lipid in the propofol preparation are metabolized by two different pathways: the citric acid cycle, where free fatty acids are oxidized to $CO_2 + O_2$; and ketogenesis to form ketone bodies. When oxygen supply and mitochondrial ATP concentration are sufficient, ketogenesis increases.²⁸ Although ketone bodies act normally as water-soluble tissue fuels, ketoacidosis can be induced when excessive production of ketone bodies depletes the alkali reserve.

In conclusion, we found that hypoxia caused high arterial propofol concentrations and reduced clearance. These changes could be induced through reduced hepatic blood flow and a lowered energy state of liver mitochondria. Hyperoxia, on the other hand, increased total ketone body concentration in arterial blood.

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