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Pulmonary Uptake of Propofol in Cats

Effect of Fentanyl and Halothane

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Background: Many drugs are removed by the lung. The pulmonary uptake of one drug can be inhibited when a second, highly accumulated drug is administered parenterally or as a chronic oral treatment. The effect of inhalational anesthetics on pulmonary drug uptake has not been extensively studied and may alter pharmacokinetics of intravenously administered drugs.

Methods: The uptake of propofol by the lung during a single passage through the pulmonary circulation was studied in four groups of anesthetized cats: spontaneously breathing cats (control group, $n = 6$), cats whose lungs were mechanically ventilated ($n = 6$), and cats whose lungs were mechanically ventilated and that were anesthetized with 1% ($n = 6$) or 1.5% ($n = 6$) halothane. In an additional group, the single-pass pulmonary uptake of propofol was studied in six spontaneously breathing cats pretreated with fentanyl. The amount of propofol taken up by the lung during the first pass was measured from double indicator-dilution outflow curves using indocyanine green (ICG) as the intravascular reference indicator.

Results: The first-pass uptake of propofol (mean \pm SEM) was $61.3 \pm 4.9\%$ and $60 \pm 3.7\%$ of the injected dose in control cats and in cats whose lungs were mechanically ventilated, respectively. Although exposure of the animals to 1% halothane had no significant effect on pulmonary extraction of propofol, the first-pass uptake decreased significantly to $38.8 \pm 6.9\%$ in cats exposed to 1.5% halothane compared with control cats and to cats undergoing mechanical ventilation of the lungs without exposure to halothane. Also, in animals pretreated with fentanyl, propofol uptake was reduced to $40 \pm 5\%$ compared with the control group.

Conclusions: The results demonstrate a substantial extraction of propofol by the lung that is not affected by mechanical ventilation. Inhibition of propofol uptake by 1.5% halothane and by fentanyl provides a potential mechanism of drug-drug interaction that may interfere with the pharmacokinetic profile of propofol, and may alter the amount of propofol needed to achieve or supplement a given depth of anesthesia. (Key words: Anesthetics, intravenous: fentanyl; propofol. Anesthetics, volatile: halothane. Lung: drug uptake. Pharmacokinetics: interaction.)

EARLY studies by Bakhle and Vane¹ emphasized the importance of the lung in the formation and inactivation of locally released mediators and circulating endogenous substances. Later studies indicated that the lung plays an active role in the uptake and metabolism of drugs.²⁻¹¹ Lipid-soluble basic drugs are extensively removed from the blood as the drug passes through the pulmonary circulation.³⁻⁷ The removal process appears to have a saturable component and involves primarily simple diffusion.^{4,5,9,12-14}

Pulmonary uptake of only a few anesthetic agents have been studied. *In vivo* experiments have demonstrated extensive first-pass pulmonary uptake of the opioids fentanyl,^{6,15,16} alfentanil,¹⁶ and meperidine,⁶ and of the local anesthetics lidocaine^{10,11} and bupivacaine.¹² As expected from their physicochemical characteristics, both the nonbasic lipophilic drug, thiopental,⁷ and the basic but nonlipophilic drug, morphine,⁶ are accumulated less by the lung.

The presence of a basic lipophilic drug has been reported to decrease the accumulation of a second drug by the lung.^{5,12,15} Rothstein *et al.*¹² demonstrated, in anesthetized rabbits, a decrease in pulmonary extraction of bupivacaine from 81 to 70% when propranolol was injected before bupivacaine. Roerig *et al.*¹⁵ found uptake of fentanyl to be 53% of the injected dose in patients receiving chronic propranolol treatment, compared with uptake of 83% in patients who received no other drugs before the study. This inhibition of drug uptake could produce a significant elevation in circu-

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lating blood levels of a drug previously removed by the uninhibited lung and, thus, precipitate toxicologic and/or unexpected pharmacologic effects.

Although volatile anesthetics are introduced through, and, thus, reach their highest concentrations in, the respiratory system, little is known about their effect on lung metabolic activity. Experimental studies have indicated that halothane inhibits norepinephrine and 5-hydroxytryptamine removal from the pulmonary circulation in rat lung perfused *in situ* and in isolated rabbit lung.¹⁷⁻¹⁹ Moreover, enflurane and isoflurane inhibit pulmonary uptake of 5-hydroxytryptamine¹⁹ and nitrous oxide inhibits norepinephrine uptake.¹⁸ However, the effect of inhalational anesthetics on pulmonary drug uptake under controlled conditions is not known.

Propofol (2,6 diisopropylphenol) is a highly lipophilic anesthetic agent, notable for its rapid onset and brief duration of action.²⁰⁻²² It has gained popularity as an intravenous anesthetic and is used for induction of anesthesia, for maintenance by continuous infusion in prolonged surgery, and for sedation in intensive care units.²³⁻²⁶ Metabolism of propofol is rapid and is primarily hepatic, but because total body clearance exceeds the putative liver blood flow, an extrahepatic component, *i.e.*, lung, is thought to contribute to its rapid elimination.^{20,22,27,28} We, therefore, assessed the uptake of propofol during a single passage through the lung, and examined the effect of halothane on the pulmonary uptake of this drug. In addition, because a pharmacokinetic interaction has been observed when propofol was used in conjunction with fentanyl,²² the current study examined the influence of fentanyl pretreatment on the pulmonary uptake of propofol.

In this study, the first-pass uptake is defined as the loss of drug from blood after a single passage through the lung, which is the net result of uptake of the drug into lung tissue and back diffusion of the drug from the lung into the intravascular space.

Materials and Methods

Animal Preparation

This protocol was approved by the Institutional Animal Care and Use Committee. Thirty cats, weighing 2.1–4.2 kg, were studied. The cats were anesthetized with pentobarbital sodium, 20 mg/kg intravenously, were secured in the supine position to a fluoroscopic table, and breathed room air spontaneously through a cuffed endotracheal tube. Polyethylene catheters were inserted into the femoral vein and femoral artery, and

into the aorta *via* the contralateral femoral artery. Another catheter was advanced, under fluoroscopic guidance, from the external jugular vein into the pulmonary artery (PA). The femoral and pulmonary arterial catheters were connected to Sorenson disposable transducers zeroed at the right atrial level, and mean pressures, obtained by time-weighted electronic integration, were continuously recorded on a Gould Recorder (Cleveland, OH).

Arterial blood gases and pH were measured at frequent intervals during the experiments (178PH, blood gas analyzer, Corning Glass Works, Medfield, MA) and sodium bicarbonate was used when necessary to maintain a pH of 7.35–7.45.

The animals' blood was anticoagulated with heparin (300 μ /kg intravenously) to facilitate blood sampling for indicator dilution studies.

Indicator Dilution Measurements

Propofol first-pass uptake was measured using a double-indicator dilution technique previously described by Roerig *et al.*⁶ An injectate containing the intravascular marker indocyanine green (ICG), (2 mg Cardiogreen; Hynson, Westcott & Dunning, Baltimore, MD), and propofol (Diprivan, 1.0 mg/kg) was prepared immediately before injection. Indocyanine green is not taken up by the lung, but remains in the intravascular space. It was used as the intravascular reference indicator and for the measurement of cardiac output. The PA catheter was repositioned by pulling it back to the right ventricle before the injection. The solution (2 ml) was injected rapidly within 2 s into the right ventricle. Arterial blood was simultaneously withdrawn from the aorta at a fixed rate (60 ml/min) by means of a Harvard model 1210 peristaltic pump (South Natick, MA) connected to an escargot-type fraction collector, and blood samples collected at the rate of 1 sample/s for 30 s.

After collection, the samples were gently mixed and then 0.1 ml of each blood sample was diluted with 1 ml of distilled water, vortexed vigorously, and centrifuged for 20 min at 2,100 rpm. The supernatant was assayed for ICG concentration in a Beckman DU-65 spectrophotometer (Irvine, CA), at 805 nm. Standard curves were constructed by adding various amounts of the injectate to blood samples collected before the appearance of ICG or drug.

The remaining 0.9-ml blood samples were centrifuged (10 min, 1,500 rpm), after which the plasma was frozen and stored at -30° C while awaiting propofol analysis. Plasma propofol concentrations were

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measured by a high-pressure liquid chromatography (HPLC) technique described by Vree.²⁹ Briefly, plasma samples (250 μ l) were mixed vigorously with 250 μ l acetonitrile (ACN) and centrifuged at 11,400 g for 15 min. Twenty-microliter aliquots of the supernatants were injected into a 25-cm \times 4.6 mm I.D. Spherisorb S50DS octadecyl Hi-Chrom HPLC column (Regis, Morton Grove, IL). The mobile phase (ACN: water: methanol, 50:40:10) was maintained at a flow rate of 2 ml/min. The pump, UV detector (set at 270 nm), and data reduction unit were manufactured by Shimadzu Corp. (Columbia, MD). Each experiment had its own recovery standard, made by adding known amounts of propofol to control blood samples.

In vitro experiments were performed to examine a possible effect of halothane on blood cell extraction of propofol. Ten milliliters of heparinized whole blood from a cat were placed in a 200-ml round-bottom flask. The flask was swirled constantly in a 37° C bath with 500 ml/min flow of breathing air, either with halothane (1%, n = 5 or 1.5%, n = 5) or without halothane (control, n = 5), passing over the blood. After 1 h, 1 ml of the blood was transferred into a tube containing 2 ml n-hexane for halothane assay. Twenty microliters of Diprivan (propofol, 10 mg/ml) were added to 5 ml of the blood, mixed thoroughly, and placed for 2 min in a shaking 37° C bath. The tube was then uncapped and kept at room temperature for 30 min. The blood was then remixed and aliquots taken for whole-blood propofol assays (3 \times 0.25 ml) and plasma separation (3 \times 1 ml, centrifuged at 5° C for 25 min at 2,500 g). The whole blood samples and 0.25 ml of each plasma sample were deproteinized by 0.25 ml acetonitrile. The 15-min, 11,400-g deproteinized supernatants were assayed for propofol by HPLC as described above, and plasma:whole-blood concentration ratios were calculated. The hematocrit was not significantly different among the groups and averaged 32 \pm 2%, which was in the range usually observed in normal cats (28–36%). There were no significant differences in plasma:whole blood concentration ratios between control samples (1.0 \pm 0.2), blood exposed to 1% halothane (1.1 \pm 0.1), and blood exposed to 1.5% halothane (0.9 \pm 0.1).

Experimental Protocol

Experiment 1: Effect of Halothane. We studied pulmonary propofol uptake in four groups. A spontaneous breathing control group (n = 6) was allowed to stabilize for 30 min following preparation. In the second group (ventilation group, n = 6), the lungs were

mechanically ventilated (Harvard ventilator) *via* a cuffed endotracheal tube; respiratory rate was set to 20 breaths/min and tidal volume (15–20 ml/kg) was adjusted to maintain arterial carbon dioxide tension between 30 and 45 mmHg. The inspired air was enriched with 100% oxygen. In the third and fourth groups, the lungs were ventilated with 1% (n = 6) or 1.5% (n = 6) halothane in oxygen. One hour was allowed for stabilization before the measurements in the latter three groups.

Arterial blood halothane concentrations were monitored by gas chromatography (RA Van Dyke, personal communication). Briefly, 1-ml whole blood samples were extracted by 2 ml n-hexane; aliquots were analyzed on a Varian 3740 gas chromatographer equipped with electron capture detector (ECD), using a 6' \times 0.125" O.D. stainless-steel column packed with 4% carbowax 400 on 80–100 mesh Poracil C (Bellefonte, PA), at 110° C. The mobile phase was 5% methane in argon. Mean arterial halothane concentrations were measured every 15 min after ventilation with halothane. These concentrations increased over 45 min and were unchanged at 60 min. Mean arterial halothane concentrations just before the experimental measurements were 160 \pm 9 μ g/ml (1% halothane) and 225 \pm 10 μ g/ml (1.5% halothane). Halothane administration caused a decrease in arterial blood pressure to about 60–70% of baseline, and this was treated with intravenous fluid administration, to a pressure of 75–90% of baseline.

Experiment 2: Effect of Fentanyl. The uptake of propofol in the presence of fentanyl was also studied using the same model as described above. In six spontaneously breathing animals, the single pass pulmonary uptake of propofol was measured 1 min after injection of fentanyl 1 μ g/kg.

Calculations

Fractional concentrations (FC) of ICG or propofol recovered in each arterial blood sample were calculated as the measured concentration divided by the total amount injected. Paired propofol and ICG outflow curves were plotted as a function of time after injection. To correct for recirculation, a semilog plot of the FC *versus* time was constructed. The linear descending portion of each curve was extrapolated by linear regression and the values of FC, corrected for recirculation, were obtained from the extrapolated lines.

The first-pass uptake of propofol up to the point of 95% passage of the ICG was calculated, as described

by others,^{6,11} from the difference in area under the ICG curve and propofol curve divided by the area under the dye curve at 95% ICG recovery. This is the fraction of injected propofol extracted from the blood by the lung at the time when 95% of the injected ICG had passed through the lung.

Instantaneous extraction ratio in each 1-s sample was calculated as:

$$\text{Extraction} = \frac{FC_{\text{ICG}} - FC_{\text{propofol}}}{FC_{\text{ICG}}}$$

Cardiac output was calculated from the injected dose of ICG divided by the area under the ICG concentration *versus* time curve, corrected for recirculation.

Statistical Analysis

Values were expressed as mean \pm SEM.

One-way ANOVA and Student's *t* test were used for statistical comparisons. Differences were considered significant at $P < 0.05$.

Results

Experiment 1: Effect of Halothane

A pair of typical outflow curves from three animals, each representing a different group, are shown in figure 1. The corresponding instantaneous extraction ratio-time curves for the same animals are shown in figure

2. After injection of propofol into the spontaneously breathing cat, there was an extensive extraction of propofol relative to ICG, as manifested by its lower peak concentration and less steep upslope (fig. 1a). For the cat illustrated in figure 1a, the first-pass pulmonary uptake of propofol was 64%, *i.e.*, 64% of the injected dose of propofol was removed during its first pass through the lung. The instantaneous extraction-time curve from this experiment, illustrated in figure 2a, shows the extraction of propofol to be greater than 90% initially, with a subsequent gradual decrease, indicative of back diffusion of the drug out of the lung into the circulation. In all experiments, the peak concentration of the propofol curve was delayed (1–3 s) with respect to that of the ICG curve (table 1), also a reflection of back diffusion of the drug out of the lung.^{6,14} Despite this back diffusion, the extraction ratio remained positive during most of the first pass, implying that the pulmonary uptake of propofol dominated its efflux back into the vascular space. The mean first-pass uptake of propofol in the control group was $61.3 \pm 4.9\%$.

Figures 1b and 2b show the first-pass uptake and instantaneous extraction ratio of propofol in a cat whose lungs were mechanically ventilated. The first-pass uptake for that cat was 62% and the mean for this group was $60 \pm 3.7\%$, which was not statistically different from the control group.

The effects of mechanical ventilation and halothane

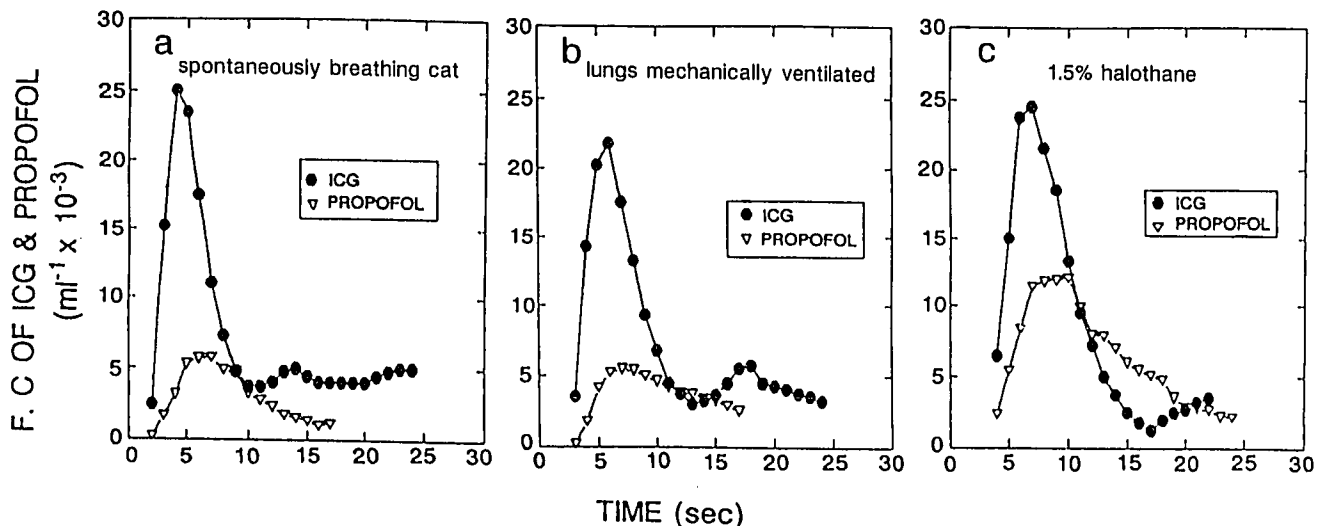


Fig. 1. Typical ICG and propofol outflow curves from three representative experiments, one from each group. On the ordinate are the fractional concentrations of ICG and propofol; on the abscissa, time from bolus injection. First-pass uptake of propofol was calculated up to 95% first-pass passage of ICG. Data indicated that 64% (A), 62% (B), and 31% (C) of the injected propofol were taken up by the lung during the first pass.

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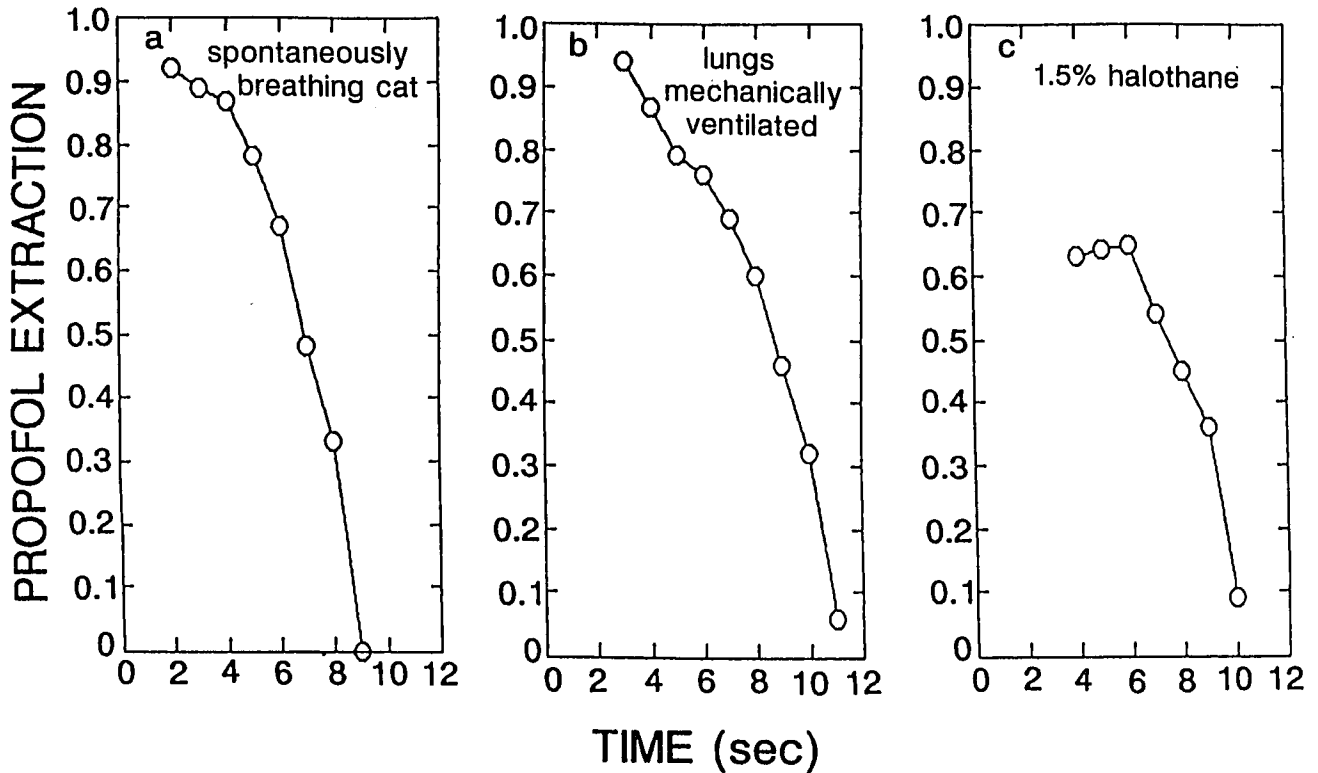


Fig. 2. Instantaneous extraction ratio of propofol as function of time from three representative experiments (A, B, C), one from each group, corresponds to the experiments in figure 1. Initial extraction was > 90% in the spontaneously breathing and ventilated cats but < 70% in the halothane exposed cat.

anesthesia on propofol uptake are shown in table 1. The first-pass uptake of propofol in cats whose lungs were ventilated with 1% halothane was slightly, but not significantly, reduced. However, in the 1.5%-halothane group, the mean uptake decreased by approximately one-third compared with the control group and to animals whose lungs were mechanically ventilated ($P < 0.05$), and averaged $38.8 \pm 6.9\%$. An example of

the first-pass uptake of propofol through the lung in one cat from the 1.5% halothane group is illustrated in figure 1c; in this case, only 31% of the injected propofol was taken up by the lung during its first pass. Figure 2c shows the instantaneous fractional extraction in the same cat. The curve shows the same pattern, *i.e.*, a concave downward curve, as in the control group, but the initial extraction ratio was lower (<70%) (P

Table 1. Effect of Halothane and Ventilation on Lung Uptake of Propofol

	N	CO ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	FPU (%)	ICG Peak Times (mean \pm SD, s)	Propofol Peak Times (mean \pm SD, s)	Peak Time Difference (range, s)
Control group	6	117 ± 17	61.3 ± 4.9	4.8 ± 0.3	6.8 ± 0.4	1-3
Mechanically ventilated animals	6	107 ± 8	60.0 ± 3.7	4.7 ± 0.2	5.8 ± 0.3	1-3
1% halothane	6	95 ± 18	53.7 ± 3.0	$7.3 \pm 0.8^*$	$9.0 \pm 1^*$	1-3
1.5% halothane	6	89 ± 13	$38.8 \pm 6.9^*$	$7.7 \pm 0.7^*$	$9.8 \pm 0.7^*$	1-3

N = number of cats in the group; FPU = first pass uptake; CO = cardiac output; ICG = indocyanine green.

* Significantly different from control group and animals in which the lungs were mechanically ventilated, $P < 0.05$.

Table 2. Blood Gas Tensions and Pulmonary Artery Pressures (PAP) from the Different Groups

	Arterial P _O ₂ (mmHg)	Arterial P _{CO} ₂ (mmHg)	PAP (mmHg)
Control group	90 ± 2	34 ± 1.3	9.3 ± 1.0
Mechanically ventilated animals	565 ± 22*	34 ± 1.8	9.5 ± 0.8
1% halothane	517 ± 13*	32 ± 1.9	9.1 ± 0.6
1.5% halothane	559 ± 23*	35 ± 2.0	9.7 ± 1.5
Fentanyl group	96 ± 4	35 ± 1.8	9.4 ± 1.0

* Significantly different from control group, $P < 0.05$.

< 0.05) compared with the control group and the group whose lungs were mechanically ventilated without halothane.

In the control group, the time of peak ICG and propofol concentrations were 4.8 ± 0.3 s and 6.8 ± 0.4 s, respectively, with no significant change in animals whose lungs were mechanically ventilated. The corresponding numbers for the 1% and 1.5% halothane groups were significantly different from the other two groups, reflecting a prolonged transit time for both tracers (table 1). However, the peak-to-peak delay, *i.e.*, the difference in time between dye concentration peak and drug concentration peak, was in the same range, 1–3 s, in all groups. This delay is related to back diffusion of the accumulated drug.⁶

As expected, cardiac output was reduced in the halothane groups compared with the other two groups, but there was no statistically significant change in this parameter among the four groups (table 1).

Blood gas measurements of the different groups in this study are shown in table 2. With ventilation, there was a significant increase in arterial oxygen tension, but it was not significantly different from arterial oxygen tensions measured in the halothane groups. Mean pulmonary arterial pressures were not significantly different among the four groups (table 2).

Experiment 2: Effect of Fentanyl

Figure 3 shows a pair of typical outflow curves with the instantaneous extraction ratio–time curve superimposed in one cat from the fentanyl group. In this cat, the uptake was only 30% of the injected dose, and, for all cats in this group, the mean first-pass uptake was $40 \pm 5\%$, which was significantly less than that for the control group ($P < 0.05$). The initial extraction ratio

was $< 75\%$ and declined as observed in the other groups. Cardiac output averaged 110 ± 10 ml · kg⁻¹ · min⁻¹ and was not significantly different from controls.

Discussion

Propofol Uptake in Spontaneously Breathing Cats: Effect of Fentanyl

The results of our study demonstrate the temporary removal of a significant portion of an intravenous dose of propofol by the lung. During the first pass through the lung, 61% of the injected propofol was taken up. Propofol fractional extraction was initially very high—indicative of extensive translocation of the drug from the blood into the lung—and then decreased rapidly to zero during the first pass through the lung. The decrease in extraction ratio, together with the delay in the peak aortic blood concentration of propofol compared with that of ICG, indicates that some of the drug left the lung rapidly returning to the circulation by back diffusion, as the concentration in blood decreased. However, at the end of the first pass, 61% of the injected propofol remained in the lung.

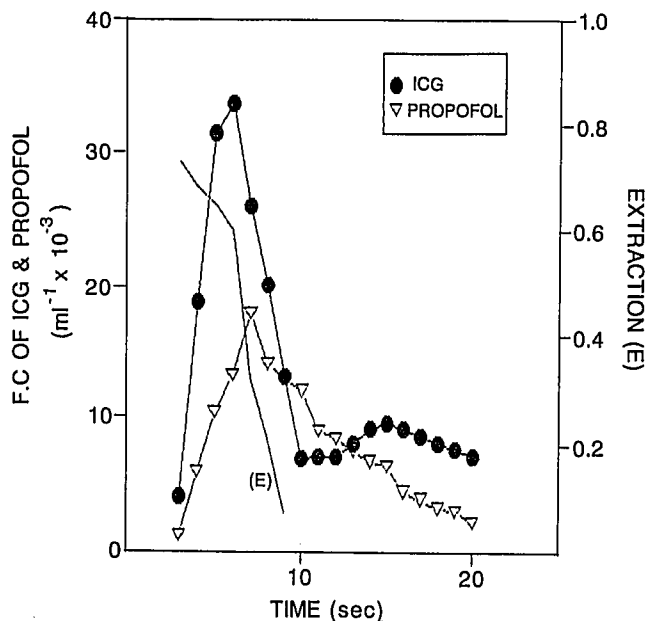


Fig. 3. Typical ICG and propofol outflow curves in a fentanyl-pretreated animal. Instantaneous extraction time curve (E) is superimposed. Data indicated that 30% of the injected propofol were taken up by the lung during the first pass. Initial extraction was $< 75\%$.

Propofol is metabolized to water-soluble conjugates of the parent compound.²⁸ Enzymes responsible for the conjugation of phenols have been postulated to be present in the lung of different species.³⁰ The liver is the major organ of elimination, but, because total body clearance of propofol exceeds the capacity of the liver with respect to its blood flow, it has been suggested that another organ may be involved in the elimination of propofol from the blood.^{20,22,27,28} Because the lung receives the entire cardiac output, even a small pulmonary extraction ratio can account for a significant clearance. Mather *et al.*,²⁷ in their study of regional propofol pharmacokinetics during intravenous infusion to adult merino ewes, showed a substantial pulmonary clearance of propofol. Thus, it is possible that, following pulmonary extraction, the drug may return to the blood from the lung at a rate yet to be determined, or be metabolized in the lung. Although this analysis is largely speculative, it may help to explain some of the pharmacokinetics and drug interactions observed when propofol is administered in conjunction with other drugs.

Previous studies have reported that 71–75% of the injected dose of fentanyl^{6,16} was removed by the lung. Accordingly, a pharmacokinetic interaction could take place when propofol is given in conjunction with the opioid. Clinical experience indicates that, when fentanyl and propofol are administered together, there is a greater incidence of apnea, and it takes longer for the patients to open their eyes.^{22,31} It has also been suggested that a pharmacokinetic interaction between the opioid and propofol is at least partially responsible for this observation. Prys-Roberts, using the Cremophor formulation of propofol (Prys-Roberts C, Adam HK, unpublished observations), and Cockshott,²² using the emulsion formulation, found significantly higher propofol blood concentrations in patients pretreated with fentanyl compared with those who did not receive the opioid. We found that propofol uptake by the lung was significantly reduced in animals receiving fentanyl compared with controls. These data may directly reflect inhibition of pulmonary drug uptake by the presence of a second, highly accumulated drug. Although the mechanism underlying this interaction is not clear, this study described a potentially important clinical interaction between two commonly used drugs. Thus, the doses of propofol necessary to achieve a given depth of anesthesia may be smaller in patients pretreated with fentanyl, irrespective of fentanyl's contribution to the level of hypnosis.

Propofol Uptake in the Presence of Halothane

Previous studies are conflicting or unclear about whether inhalational anesthetics can affect pulmonary extraction of drugs. Jorfeldt *et al.*⁸ studied the pulmonary uptake of lidocaine in patients during surgical anesthesia. There was no significant difference in the pulmonary uptake of lidocaine between the awake and anesthetized patients. Nevertheless, Jorfeldt *et al.* reported that there was a significant low extraction in the anesthetized group at some time points during the first pass of lidocaine through the lung. These patients received fentanyl in addition to other drugs, their lungs were ventilated, and anesthesia was maintained with nitrous oxide. Therefore, no conclusion can be drawn regarding the effect of the inhalational anesthetics on pulmonary lidocaine uptake. Pulmonary uptake of propranolol in dogs has been studied by Pang *et al.*³² They found an increase in the pulmonary extraction of propranolol in dogs anesthetized with thiopental, nitrous oxide, and fentanyl, and a further increase in another group of dogs in which anesthesia was induced and maintained by thiopental, nitrous oxide, and halothane (0.5–1%). The effect of ventilation on propranolol uptake by the lung was not assessed in these experiments, and the duration of exposure of the animals to halothane before injection of propranolol was unclear. We found that the first-pass uptake of propofol by the lung was significantly reduced in cats exposed for 1 h to 1.5% halothane compared with control group and the group whose lungs were mechanically ventilated without halothane. In contrast, the uptake of propofol in animals anesthetized with 1% halothane was not significantly different from the control group and mechanically ventilated group without halothane. Finally, there were no significant differences in pulmonary uptake of propofol between control (spontaneously breathing) and mechanically ventilated (without halothane) groups of animals.

The change in propofol first-pass uptake, as determined by indicator-dilution outflow curves, in animals exposed to 1.5% halothane, may be caused by one or more of the following mechanisms: 1) changes in pulmonary blood flow, 2) change in capillary surface area due to lung inflation, 3) change in arterial blood gas tension, and 4) a direct effect of halothane on pulmonary endothelial cell function and structure. With respect to mechanism 1, several studies have investigated the effect of cardiac output on pulmonary drug uptake and the interplay between blood flow and vascular surface area on lung metabolic activity. In awake

sheep, pulmonary extraction of propranolol was unchanged compared with controls, despite a 3.5-fold increase in cardiac output.¹⁴ Pang *et al.*¹³ found a negative correlation between propranolol pulmonary uptake and cardiac output in dogs, but this was not statistically significant. First-pass uptake of bupivacaine,¹² fentanyl,⁶ verapamil, and diazepam⁷ have been found to be independent of cardiac output. In the current study, cardiac output was not significantly reduced in the halothane groups compared with controls, and cannot explain the reduced pulmonary uptake of propofol observed in cats exposed to 1.5% halothane. Therefore, it is unlikely that the change in uptake is caused by altered pulmonary blood flow. It cannot be ruled out, however, that redistribution of pulmonary blood flow, induced by halothane, at the regional or microvasculature level may be a factor in the decreased uptake.

To study the effect of halothane *per se* on pulmonary drug extraction in an *in vivo* experiment, it is necessary to ventilate the lungs of the animal. In this case, no conclusions can be drawn when comparing drug uptake in spontaneously breathing cats *versus* cats whose lungs were mechanically ventilated. Therefore, in addition to the control group, we studied propofol uptake in animals whose lungs were mechanically ventilated. Changes in surface area, induced by lung inflation³³ (mechanism 2, above), may have caused the decrease in propofol uptake. We found that pulmonary propofol uptake was not significantly different in the control group compared with the group whose lungs were mechanically ventilated. Accordingly, we concluded that ventilation does not account for the impaired propofol uptake observed in the halothane group.

Abnormalities in arterial gas tensions (mechanism 3) may affect lung metabolism by changing blood flow or surface area (hypoxic pulmonary vasoconstriction), or by a direct toxic effect *via* oxygen-free radical production.³³⁻³⁹ However, with the exception of higher oxygen tensions, which were observed in both halothane-anesthetized animals and animals whose lungs were mechanically ventilated without exposure to halothane, there were no significant differences in arterial blood gas tensions or mean pulmonary artery pressures between groups. Therefore, changes in blood gas tensions cannot explain the effect of halothane on the uptake of propofol by the lung in our experiments.

Mechanism 4, above, covers a broad spectrum of effects that halothane exerts at the cellular level. It is possible that these effects are not confined to central

nervous system cells, but are exerted in endothelial and other cell types as well. Previous studies showed that halothane inhibits pulmonary uptake of norepinephrine¹⁸ and 5-hydroxytryptamine¹⁹ in isolated perfused lungs. The effect of halothane was exerted at the transport step, *i.e.*, the active, Na⁺-dependent transport of 5-hydroxytryptamine into pulmonary endothelial cells.¹⁹ Unlike norepinephrine and 5-hydroxytryptamine, pulmonary drug removal does not depend on active transport. Passive diffusion into pulmonary endothelial cells is the predominant mechanism for drug uptake, although a small component of saturable binding site has been demonstrated for a few drugs.^{4,5,9,12-14} The exact mechanism by which halothane reduced propofol removal by the lung in our experiments is unclear. It is plausible that the interference exerted on the membranes of neurons in the central nervous system by halothane can also be exerted on membranes of other cells exposed to the anesthetic, resulting in an impairment of transport and uptake processes. Further studies are required to define the exact mechanism.

The applicability of these data to the clinical situation may be limited because propofol was administered during halothane anesthesia. However, for patients who receive a volatile agent for a few hours, additional propofol may be given before emergence, and, in these cases, halothane-propofol interaction might be clinically relevant. Moreover, the results of our studies may have significant implications regarding past and future use of halothane for anesthesia in animal protocols designed to investigate the role of the lung in uptake and metabolism of highly accumulated drugs.

In summary, pulmonary extraction of propofol in cats is substantial, sufficient to reduce the amount of drug available for distribution, with a consequent delay in the time needed to reach maximum clinical effect. The inhibition of propofol uptake by fentanyl will allow more of the drug to enter the systemic circulation after a bolus injection. The 20% decrease in the first-pass uptake of propofol observed in this study may account for some of the pharmacologic effects observed during the clinical use of fentanyl-propofol anesthesia. High concentrations of halothane also inhibit propofol uptake by the lung. Decreased uptake in the 1.5% halothane group was not associated with decreased cardiac output. Therefore, the site of action of halothane inhibition may lie in cell membranes and, as a result, halothane may also modify the pulmonary uptake and early pharmacokinetics of other highly accumulated drugs.

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