Pharmacokinetics of intravenous emulsified isoflurane in beagle dogs

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Editor’s key points
• The safety and efficacy of i.v. emulsified isoflurane inducing anaesthesia in animals were demonstrated in this study.
• A pharmacokinetic analysis showed that a two-compartment model best describes the data.
• The pharmacokinetic parameters for bolus i.v. injection differ from those for continuous i.v. infusion.
• Infusion results in an increase in the blood/gas partition coefficient of isoflurane which increased influences kinetics.

Background. We previously demonstrated that i.v. emulsified isoflurane induces general anaesthesia in animals. In this study, we compared the pharmacokinetics of emulsified isoflurane given as i.v. bolus and as infusion in beagle dogs.

Methods. Sixteen beagle dogs were assigned randomly to a bolus group comprising three subgroups and an infusion group. The three bolus subgroups received 120, 150, or 180 mg kg\(^{-1}\) of isoflurane and the infusion group received isoflurane at 12 mg kg\(^{-1}\) min\(^{-1}\) for 150 min. Isoflurane concentrations were determined by gas chromatography. The parameters involved in the pharmacokinetic model were calculated using the DAS ver1.0 software.

Results. A two-compartment model best described the data in both bolus and infusion groups. The half-lives of distribution \([t_{1/2a}]: 1.77 (0.57)\) min and elimination \([t_{1/2b}]: 17.66 (5.56)\) min in the bolus group were shorter than those in the infusion group \([14.12 (4.04)\) min, 58.21 (11.39) min, \(P<0.01)\]. The apparent volume of the central compartment \([V_c]: 0.377 (0.138)\) litre kg\(^{-1}\) in the bolus group was less than that in the infusion group \([0.809 (0.077)\) litre kg\(^{-1}\), \(P<0.01)\]. The total body clearance \([Cl]: 0.043 (0.032)\) litre kg\(^{-1}\) min\(^{-1}\) in the bolus group was greater than that in the infusion group \([0.028 (0.008)\) litre kg\(^{-1}\) min\(^{-1}\)\].

Conclusions. A two-compartment model adequately describes the pharmacokinetics of emulsified isoflurane for both bolus and infusion. The resulting kinetic parameters differ mainly because of the increasing blood/gas partition coefficient and the sustained nature of the isoflurane partial pressure during infusion.

Keywords: dog; emulsified isoflurane; pharmacokinetics; volatile anaesthetic

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The safety and efficacy of volatile anaesthetic agents administered i.v. in a lipid emulsion have been demonstrated.\(^{1–7}\) Recently, our group found that the optimal concentration of emulsified isoflurane in 30% Intralipid is 120 mg ml\(^{-1}\) and \(ED_{50}\) and \(LD_{50}\) for i.v. injection in rats are 0.072 ml kg\(^{-1}\) and 0.216 mg kg\(^{-1}\), respectively.\(^8\) We also measured the minimum alveolar concentration (MAC\(_{i.v.}\), 1.12%) of emulsified isoflurane by i.v. infusion in dogs,\(^9\) which was lower than the MAC value (1.38%) when isoflurane was administered by inhalation. In other studies, we showed that i.v. emulsified isoflurane can produce cardioprotection against myocardial ischaemia and reperfusion injury in rats.\(^5\)\(^ 6\)\(^ 10\)

When emulsified isoflurane was used for epidural anaesthesia in rats, it also produced anaesthetic effects.\(^11\) Besides cardiac muscle, the protective effects of emulsified isoflurane have been found for the liver and the lungs in rats.\(^12\) In a recent study, we proved that emulsified isoflurane acts synergistically with lidocaine in i.v. regional anaesthesia in rats.\(^13\)

Such results imply that emulsified isoflurane may have important clinical applications and offer some advantages: it may facilitate a rapid sequence induction; allow maintenance of anaesthesia without a vaporizer; and provide sedation in the intensive care unit. In addition, it may provide a good choice for some short operations such as anaesthesia for outpatients by bolus administration. From the foregoing points, both bolus injection and continuous infusion of emulsified isoflurane may be very useful in clinical practice. However, its pharmacokinetic characteristics are lacking. We designed this study in beagle dogs to address such concerns.
Methods

Preparation of emulsified isoflurane solution

Isoflurane was obtained from Abbott Laboratories (Queenborough, Kent, UK). One day before the experiment, using an aseptic technique, a solution of isoflurane was prepared as follows: 18.4 ml of 30% Intralipid® (Sino-Swed Pharmaceutical Corp. Ltd, Wuxi, Jiangsu, China) and 1.6 ml of liquid isoflurane were transferred into a 20 ml glass ampoule using syringes, and the ampoule was sealed with an alcohol blowtorch. Subsequently, the ampoule was vigorously shaken on a vibrator for 15 min to equilibrate isoflurane with the lipid emulsion. Using this technique, 50 ampoules of emulsified isoflurane (120 mg ml⁻¹) were prepared for this study.

To ensure safety for i.v. administration, isoflurane concentration in lipid emulsion used in this study was set at about 80% of the saturated concentration in Intralipid®, 30% for isoflurane, which was based on its solubility in Intralipid® 30% and its vapour pressure at room temperature. Before this experiment, the stability of this preparation was investigated. No lipid droplets were found during 6 months of storing at room temperature (20–26 °C). The measured concentration of isoflurane at 3 h after the emulsified isoflurane was transferred into a syringe was not different from its original concentration.

Experimental protocol

All the protocols were approved by the Institutional Animal Care and Use Committee of Sichuan University (Chengdu, Sichuan, China). Sixteen healthy beagle dogs weighing 9.5–12.5 kg and aged 9–12 months were chosen and randomly assigned to the bolus group (comprising three subgroups, four dogs in each group) and the infusion group (four dogs). Doses of emulsified isoflurane for the two groups were based on the results from our previous studies. In one previous study determining the median effective dose (ED₅₀) of emulsified isoflurane in beagle dogs by bolus i.v. injection, we found that the ED₅₀ needed to produce the loss of righting reflex was 112.8 mg kg⁻¹ and that the arterial pressure decreased sharply when the injection dose exceeded 180 mg kg⁻¹. In order to limit the effects of haemodynamic changes on the pharmacokinetics of i.v. emulsified isoflurane, 120 mg kg⁻¹ (slightly more than 1 ED₅₀) and 180 mg kg⁻¹ were chosen for two subgroups as the low and the high bolus doses, respectively. An intermediate dose (150 mg kg⁻¹) was used for another subgroup’s bolus injection. During the determination of the minimum alveolar concentration (MACₐ) of i.v. emulsified isoflurane in dogs, we found that the infusion of emulsified isoflurane at a rate of 12 mg kg⁻¹ min⁻¹ caused little or no fluctuation in arterial pressure. Therefore, this infusion rate was adopted for the infusion group in this study.

Animal instrumentation

Beagle dogs were positioned in sternal recumbency on a restraining table after body weight had been measured. Lactated Ringer’s solution was infused at a rate of 10 ml kg⁻¹ h⁻¹ into the right cephalic vein through a three-way stopcock connected to a 20 G vein needle-catheter. Heart rate, ECG, ear pulse oxygen saturation, invasive femoral arterial pressure, and end-expired isoflurane concentrations were monitored with a 150B3 monitor (Phillips, Suzhou, China).

Each dog was fitted with a special facemask connected to an anaesthesia machine (Excel 210 SE; Datex-Ohmeda, Madison, WI, USA) and breathed 100% oxygen. Anaesthesia was induced i.v. with midazolam at a dose of 0.2 mg kg⁻¹ and fentanyl 5–10 μg kg⁻¹ given in the right cephalic vein. Succinylcholine was given at 1–2 mg kg⁻¹ to facilitate tracheal intubation with an 8 Fr cuffed tracheal tube. Ventilation of the lungs was controlled and adjusted to maintain the end-tidal carbon dioxide pressure at 35–40 mm Hg. The fresh oxygen flow rate was maintained between 3 and 3.5 litre min⁻¹, which exceeded the minute ventilation volume to avoid isoflurane re-breathing. The oesophageal temperature was maintained at 36.5–38.5 °C using heating blankets. After heart rate and arterial pressure were stable for 15 min, the three bolus doses (120, 150, and 180 mg kg⁻¹) of emulsified isoflurane, prepared by an appointed person (all other investigators were blinded to which dose belonged to which subgroup), were administered via the right cephalic vein within 1 min. In the infusion group, emulsified isoflurane was continuously infused via the right cephalic vein at a rate of 12 mg kg⁻¹ min⁻¹, using a micro-infusion pump (TCI-I; Sylugao High Technology Development Co., Ltd, Beijing, China) for 150 min (total dose 1800 mg kg⁻¹ isoflurane).

During the entire experiment, anaesthesia was maintained by i.v. bolus injections of midazolam (2–3 mg), fentanyl (0.05–0.1 mg), and vecuronium (1–2 mg), as indicated by increases in arterial pressure and heart rate, or the appearance of body movement. Changes in arterial pressure, heart rate, and end-expired isoflurane concentration were recorded. If the arterial pressure decreased by more than 30% of its base value (measured before induction) for more than 2 min, 2–3 mg of i.v. ephedrine was administered to restore a normal arterial pressure.

Blood and gas sampling

Twenty millilitre glass syringes were used for sampling 4 ml of femoral arterial blood, and 10 ml glass syringes were used for sampling 5 ml of end-expired gas. The 20 ml syringes were capped with three-way stopcocks and sealed by coating the plungers with a thin layer of silicone grease. All the 20 ml glass syringes were lubricated with heparin (2.5 units ml⁻¹). To ensure that the sampled end-expired gas approximated alveolar gas, a 20 G plastic tube was put into the tracheal tube through a three-way stopcock and its inlet was placed close to the distal end of the tracheal tube. On the basis of the results of our pilot study, in the bolus group, arterial blood and end-expired gas samples were collected at 0, 1, 2, 4, 6, 12, 24, 48, and 96
min after i.v. injection. In the infusion group, femoral arterial blood and end-expired gas samples were collected at 0, 15, 30, 60, 90, and 120, 150 min during infusion and at 0.5, 1, 2, 4, 6, 12, 24, 48, 96, 120, and 150 min after termination of infusion. End-expired isoflurane concentrations were continuously monitored.

**Gas chromatography analysis**

The experimental details used to measure isoflurane concentration in the current investigation have been described previously. We used a gas chromatograph (Agilent 4890D; Tegent Technology Ltd, Shanghai, China) equipped with a flame ionization detector to measure concentrations of isoflurane. The 6 m long, 3.2 mm ID column was packed with SF-96 and its temperature was 75°C. Nitrogen at a flow rate of 17 ml min⁻¹ was the carrier gas. Stream flow was delivered through the column to a flame ionization detector supplied by hydrogen at 40 and air at 200 ml min⁻¹. An HP 3398 GC workstation (Tegent Technology Ltd) collected the gross output from the gas chromatograph and peak areas were automatically calculated.

Isoflurane blood/gas partition coefficient (λb/g) and isoflurane vapour concentration in the blood (Cb, vol%/g) were determined at 37°C by the two-stage headspace equilibration method. The equations for the calculation of isoflurane λb/g and isoflurane vapour concentration in the blood are expressed as:

\[
    \lambda_{b/g} = \left( \frac{V_{G2}}{V_{B2}} \right) \times \left( \frac{C_2}{C_1 - C_2} \right); \quad C_b = \frac{V_{G1} \times C_1 + V_{B1} \times C_b}{V_{B1} + C_b \times \lambda_{b/g}}
\]

where \( V_{G2} \) and \( V_{B2} \) are the gas volume and blood sample volume retained in the syringe for the second equilibration, \( C_1 \) and \( C_2 \) are the anaesthetic concentrations in the gas phase at the first and second equilibration, and \( V_{G1} \) and \( V_{B1} \) are the gas volume and blood sample volume at the first equilibration.

The isoflurane concentration in blood (\( C_L \), mg litre⁻¹) can be converted from its \( C_b \):

\[
    C_L = \left( \frac{C_b}{V_L} \right) \times SG \times 10000 (mg \ liter^{-1})
\]

where \( V_L \) (ml) is the gas volume of isoflurane when 1 ml of liquid isoflurane completely vaporizes into gas at the measured temperature (37°C) at 1 atm at sea level, and \( V_L = 1 \times SG/MW \times 22.400 \times (273 + 37)/273 \times C_L \), and SG and MW are the specific gravity (g ml⁻¹) and molecular weight of liquid isoflurane, respectively.

According to Henry’s law, the isoflurane concentration in blood= isoflurane partial pressure in gas phase × solubility/ BP, where BP is the barometric pressure. Thus, isoflurane partial pressure in the femoral arterial blood (Pa) was calculated by the equation \( Pa = (C_b / \lambda_{b/g}) \times 760 \) (mm Hg), where 760 is the atmospheric pressure expressed as mm Hg at sea level at 37°C. Isoflurane partial pressure in the end-expired gas (PE) equals its percentage concentration in the gas phase multiplied by 760 mm Hg.

**Data on pharmacokinetic parameters and statistical analysis**

Values throughout this article are expressed as means (SD). The pharmacokinetic models and parameters were calculated by using a special pharmacokinetic software DAS ver1.0 (Mathematical Pharmacology Professional Committee of China, Shanghai, China) to assess the changes of isoflurane concentrations in blood vs time. A two-step approach with individual fitting and reporting the statistics of the individual pharmacokinetic parameters was used in each group. One-, two-, and three-compartment models were tried for each individual, respectively. The method of weighted sum of squared of residuals (S_w) was used to judge a model, and the method of least squares was used to estimate the model parameters by minimizing S_w. The weighting coefficient was determined by the square of reciprocal concentration (\( w = 1/C^2 \)). A best model was selected by the one with smallest S_w. Residuals of isoflurane concentrations were calculated as the differences between measured isoflurane concentrations and predicted concentrations. The performance error (PE), the median PE (MDPE), and the median absolute PE (MDAPE) were also calculated in each group, where PE = [(Cm - Cp)/Cp × 100%], Cm is the measured isoflurane concentration and Cp the predicted isoflurane concentration.

One-way analysis of variance was applied to the comparison of pharmacokinetic parameters among the three bolus subgroups and the infusion group. An α-level of <0.01 was accepted as significant.

Linear regression analysis was applied to analyse the correlation between isoflurane λb/g and the infused volume of lipid emulsion. A Bland and Altman analysis was applied to analyse the correlation between the difference (PE − Pa) and their average [(PE + Pa)/2] at each corresponding time point for the two groups.

**Results**

The curve of isoflurane concentration logarithm vs time is illustrated in Figure 1. All the data of isoflurane concentrations vs time for each group are shown in Table 1. Among the three bolus subgroups, the AUCo→t (area under the curve of isoflurane concentration in blood vs time) increased proportionately with the increase in injection dose. No significant differences were found in t1/2a (half-life of distribution), t1/2b (half-life of elimination), V2 (apparent volume of the central compartment), Cl (total body clearance), or rate constants (k10, describing elimination from the central compartment to the outside; k12a, describing distribution from the central compartment into the peripheral compartment; k21b, describing redistribution from the peripheral compartment into the central compartment) among the three bolus subgroups.
Compared with the infusion group, all the data from 12 dogs in the three bolus subgroups were accounted together as the bolus group. Both the mean values of $t_{1/2a}$ and $t_{1/2b}$ in the bolus group were shorter than those in the infusion group. The mean value of $V_1$, the apparent volume of the central compartment; $Cl$, total body clearance; $AUC_0–t$, area under the curve of isoflurane concentration in blood vs time; $k_{10}$, the rate constant describing elimination from the central compartment to outside; $k_{12}$, the rate constant describing distribution from the central compartment into peripheral compartment; $k_{21}$, the rate constant describing redistribution from the peripheral compartment into the central compartment

### Table 1 Comparison of the pharmacokinetic model and parameters between the bolus group and the infusion group. Data are presented as mean (SD). The observation time in the bolus group and the infusion group is 96 and 300 min, respectively. $^*P<0.01$ vs values of the low dose. $^\dagger P<0.01$ vs mean values of the bolus group. $t_{1/2a}$, the half-life of distribution; $t_{1/2b}$, the half-life of elimination; $V_1$, the apparent volume of the central compartment; $Cl$, total body clearance; $AUC_0–t$, area under the curve of isoflurane concentration in blood vs time; $k_{10}$, the rate constant describing elimination from the central compartment to outside; $k_{12}$, the rate constant describing distribution from the central compartment into peripheral compartment; $k_{21}$, the rate constant describing redistribution from the peripheral compartment into the central compartment.

<table>
<thead>
<tr>
<th>Compartment model</th>
<th>Bolus group</th>
<th>Infusion group (n = 4)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Low dose (n = 4)</td>
<td>Median dose (n = 4)</td>
</tr>
<tr>
<td>$t_{1/2a}$ (min)</td>
<td>1.87 (0.67)</td>
<td>1.68 (0.38)</td>
</tr>
<tr>
<td>$t_{1/2b}$ (min)</td>
<td>17.12 (7.74)</td>
<td>18.01 (3.15)</td>
</tr>
<tr>
<td>$V_1$ (litre kg$^{-1}$)</td>
<td>0.380 (0.256)</td>
<td>0.385 (0.105)</td>
</tr>
<tr>
<td>$Cl$ (litre kg$^{-1}$ min$^{-1}$)</td>
<td>0.041 (0.023)</td>
<td>0.046 (0.034)</td>
</tr>
<tr>
<td>$AUC_0–96$ (mg min litre$^{-1}$)</td>
<td>3.564 (708)</td>
<td>4.437 (973)$^\dagger$</td>
</tr>
<tr>
<td>$AUC_0–\infty$ (mg min litre$^{-1}$)</td>
<td>3.743 (842)</td>
<td>4.765 (990)$^*$</td>
</tr>
<tr>
<td>$k_{10}$ (litre min$^{-1}$)</td>
<td>0.134 (0.031)</td>
<td>0.123 (0.078)</td>
</tr>
<tr>
<td>$k_{12}$ (litre min$^{-1}$)</td>
<td>0.375 (0.170)</td>
<td>0.411 (0.095)</td>
</tr>
<tr>
<td>$k_{21}$ (litre min$^{-1}$)</td>
<td>0.176 (0.059)</td>
<td>0.193 (0.046)</td>
</tr>
</tbody>
</table>

Figure 3. The MDPE and MDAPE are $-2.79\%$ and $6.79\%$ in the bolus group and $2.19\%$ and $4.90\%$ in the infusion group. Figure 4 shows the isoflurane $\lambda_{bg}$–time curves for the bolus group (example from the bolus subgroup of 180 mg kg$^{-1}$) and the infusion group. The isoflurane $\lambda_{bg}$ increased slightly after bolus i.v. injections. However, in the infusion group, isoflurane $\lambda_{bg}$ increased progressively for the whole infusion period (slope$=-0.018$) and it decreased right after the discontinuation of infusion with a lower speed (slope$=-0.010$). Figure 5 presents a positive linear correlation between isoflurane $\lambda_{bg}$ and the infused volume of lipid emulsion in the infusion group ($R^2=0.904$). The time course curves of PE and Pa for the bolus group (example from the bolus subgroup of 180 mg kg$^{-1}$) and the infusion.
group are shown in Figure 6. In the infusion group, $P_E$ and $P_a$ increased with a similar high speed for the first 15 min and with a much lower speed for the remnant period of infusion. After bolus injection or stopping infusion, both the isoflurane $P_E$ and $P_a$ are significantly decreased. Isoflurane $P_E$ correlated well with its $P_a$ for all the corresponding time points (Fig. 7). As would be expected, $P_E$ lagged behind $P_a$, but the difference was small.

**Discussion**

The results of this study indicate that a two-compartment model best describes the data for both bolus i.v. injection and continuous i.v. infusion of emulsified isoflurane in beagle dogs (Table 1). This is consistent with the results reported by Wissing and colleagues\(^\text{16}\) and Rietbrock and colleagues\(^\text{17}\) for inhaled isoflurane anaesthesia in a clinical setting.

This study also shows that the pharmacokinetic parameters for bolus i.v. injection differ from those for continuous i.v. infusion. We speculate that these differences may be explained as follows: bolus i.v. injection produces an acute peak that rapidly declines (Figs 1a and 6a). The initial distribution goes to vascular tissues (the central compartment) such as intestine and liver, but the resulting isoflurane partial pressures in these tissues are not sustained because of redistribution to tissues with lower time constants, such as muscle and fat, as reported by Price\(^\text{18}\). There is not enough time after a bolus injection for a sustained anaesthetic concentration (or partial pressure) in vascular tissues to be transmitted by intertissue distribution to adjacent tissues, such as fat (e.g. from the intestine to omental and mesenteric fat;
from the kidney to perirenal fat). In contrast, the sustained nature of the blood concentration during the relatively long infusion study (Figs 1B and 6B) allows the development of a sustained isoflurane partial pressure in vascular tissues. It allows sufficient time for the impact of intertissue diffusion to become manifest as reflected in a larger estimate of the central compartment. That is, with the infusion study, an appreciable amount of anaesthetic moves from vascular tissues to a thin layer of adjacent fat, increasing the apparent central volume into which the isoflurane distributes and resides. This explanation is consistent with the five-compartment model for inhaled isoflurane in humans reported by Eger’s group.19–22 The duration of anaesthetic application and washout in the current study was not sufficient to test three of the five compartments described by Eger’s group, particularly the muscle, fat, and intertissue distribution compartments, compartments with time constants of 2–4 h or more.

In the current study, the isoflurane $\lambda_{bg}$ increased slightly after bolus i.v. injections (Fig. 4). However, with i.v. infusion, isoflurane solubility in blood increased gradually (Figs 4 and 5). And although the isoflurane $\lambda_{bg}$ gradually decreased after the discontinuation of infusion, by the last measurement, it did not decrease to the levels before infusion. Such a changing isoflurane $\lambda_{bg}$ will affect the pharmacokinetic model and parameters of i.v. emulsified isoflurane. This greatly increases the complexity and difficulty of interpretation of the pharmacokinetics, and it can no longer be mimicked by a stationary model. The smallness of the change of isoflurane $\lambda_{bg}$ in the bolus group implies that induction of and recovery from anaesthesia would not be significantly influenced. However, in the infusion group, the increase in isoflurane $\lambda_{bg}$ may alter the rate of recovery from anaesthesia in two ways. During infusion, the isoflurane $\lambda_{bg}$ increases progressively (Figs 4 and 5). However, assuming that the infused lipid—the cause of the increase in the isoflurane $\lambda_{bg}$—does not proportionately enter tissue cells, the infusion must decrease isoflurane tissue/blood partition coefficients. By increasing the relative capacity of blood to hold isoflurane, more isoflurane can be delivered per minute to tissues and thereby will accelerate the distribution equilibration of

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**Fig 4** The change of isoflurane blood/gas partition coefficient. The isoflurane $\lambda_{bg}$ increases but slightly after bolus i.v. injections (example from high-dose subgroup). However, in the infusion group, isoflurane $\lambda_{bg}$ increases progressively for the whole infusion period (slope=0.018) and it decreases right after the discontinuation of infusion with a slower speed (slope=-0.010).

**Fig 5** The correlation of isoflurane blood/gas partition coefficient vs the infused volume of lipid emulsion. For the combined data of all cases in the continuous infusion group, a positive linear correlation existed between the infused volume of lipid emulsion and isoflurane blood/gas partition coefficient ($R^2=0.904$).
isoflurane between blood and tissues compared with the condition of ‘unchanged’ isoflurane tissue/blood partition coefficients. Similarly, during wash out, the decreased tissue/blood partition coefficients would accelerate the elimination of isoflurane from tissues to blood, and might accelerate the recovery from anaesthesia. However, an increase in isoflurane $\lambda_{bg}$ would decrease the clearance of isoflurane from blood to the lungs and thereby slow elimination. The effect of an increased isoflurane $\lambda_{bg}$ on recovery from anaesthesia would be a cumulative result of these two opposing effects. Furthermore, these thoughts suggest that isoflurane or halothane may not be ideal anaesthetics for emulsified anaesthetic delivery. Sevoflurane and desflurane have much smaller blood/gas partition coefficients, and thus they might be better choices.

In the current study, both for bolus i.v. injection (Fig. 6A) and for i.v. infusion (Fig. 6B), PE is always slightly lower than Pa during the entire uptake and elimination phases at corresponding time points, which is consistent with the result of our previous study. In Figure 7, almost all data points...
(PE – Pa) are below zero. A small bias exists in both Figure 7A and B, and the bias has an increasing trend with an increase in isoflurane partial pressure (or concentration) in blood after the infusion of emulsified isoflurane in the infusion group. The difference between PE and Pa may be caused by ventilation–perfusion abnormalities. Ventilation of poorly perfused or unperfused alveoli would decrease the end-tidal partial pressure relative to that in blood. The barrier of alveolar membrane to diffusion or the dilution of alveolar dead-space gas is also an important factor.

A lower PE indicates that the isoflurane partial pressure between alveolar gas and arterial blood has not yet achieved a complete equilibration.23 24 The gradient also implies that the anaesthetic effect-site concentration (or partial pressure) in the brain may be underestimated by the end-expired anaesthetic concentration (or partial pressure) when emulsified volatile anaesthetic agents are administered i.v.

As noted earlier, the current report has limitations, particularly in the modelling of the data. The data themselves would seem to be worthwhile because they suggest the existence of differences between the kinetics of bolus vs continuous infusions of volatile agents in emulsions. And we can speculate with some confidence on the reasons for these differences. But the modelling is hindered by its linearity, its failure to account for the effect of a changing blood/gas partition coefficient, and by the limited period of examination. Nonetheless, we suggest that the results from these models supply a qualitative indication of the differences that might be expected to be quantified in a more definitive model.

In conclusion, the pharmacokinetic parameters of isoflurane in an emulsion differ between i.v. bolus injection and i.v. infusion. Infusion results in an increase in the blood/gas partition coefficient of isoflurane, and this increase influences kinetics. Despite this limitation, the current data can be evaluated by a two-compartment model for both i.v. infusion and bolus injection. Bolus injection of emulsified isoflurane had shorter $t_{1/2Aa}$ and $t_{1/2Ba}$, smaller $V_1$, and higher Cl values than found for a continuous i.v. infusion. These differences would be consistent with the partition coefficient increasing with infusion and the sustained nature of the isoflurane partial pressure during infusion.

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Declaration of interest

None declared.

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References

5 Yang J, Chai YF, Gong CY, et al. Further proof that the spinal cord, and not the brain, mediates the immobility produced by inhaled anesthetics. Anesthesiology 2009; 110: 591–5
9 Yang XL, Ma HX, Yang ZB, et al. Comparison of minimum alveolar concentration between intravenous isoflurane lipid emulsion and inhaled isoflurane in dogs. Anesthesiology 2006; 104: 482–7
17 Rietbrock S, Wissing H, Kuhn I, Fuhr U. Pharmacokinetics of inhaled anesthetics in a clinical setting: description of a novel


20 Carpenter RL, Eger EI II, Johnson BH, Unadkat JD, Sheiner LB. Pharmacokinetics of inhaled anesthetics in humans: measurements during and after the simultaneous administration of enfurane, halothane, isoflurane, methoxyflurane, and nitrous oxide. *Anesth Analg* 1986; 65: 575–82

21 Carpenter RL, Eger EI II, Johnson BH, Unadkat JD, Sheiner LB. The extent of metabolism of inhaled anesthetics in humans. *Anesthesiology* 1986; 65: 201–5


23 Holdcroft A, Bose D, Sapsed-Byrne SM, Ma D, Lockwood GG. Arterial to inspired partial pressure ratio of halothane, isoflurane, sevoflurane and desflurane in rats. *Br J Anaesth* 1999; 83: 618–21


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