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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 [$t_{1/2\alpha}$: 1.77 (0.57) min] and elimination [$t_{1/2\beta}$: 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_1, 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.[4 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.

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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:[9] 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.[8] 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.[9 14] In one previous study determining the median effective dose (ED_{50}) of emulsified isoflurane in beagle dogs by bolus i.v. injection,[10] we found that the ED_{50} 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 ED_{50}) 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 ($MAC_{i.v.}$) of i.v. emulsified isoflurane in dogs,[9] 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 (Philips, 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; Silugao 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, femoral arterial blood and end-expired gas samples were collected at 0, 1, 2, 4, 6, 12, 24, 48, and 96