Veterinary Anaesthesia and Analgesia 2017, **xxx**, 1–9 http://dx.doi.org/10.1016/j.vaa.2016.02.004

RESEARCH PAPER

Intravenous 15% isoflurane lipid nanoemulsion for general anesthesia in dogs

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Abstract

Objective To investigate the efficacy of a new intravenous (IV) nanoemulsified isoflurane formulation for maintenance of general anesthesia in dogs.

Study design Prospective, crossover, experimental study.

Animals Seven healthy, mature, mixed-breed dogs, three male and four female, weighing 11.5 ± 1.5 kg.

Methods Anesthesia was induced with propofol for instrumentation. Measurements were obtained before administration of either inhaled isoflurane (Iso-I) or IV 15% isoflurane-loaded lipid nanoemulsion (Iso-nano). The minimum alveolar concentration (MAC) of isoflurane was determined using the 'up-and-down' technique. A tail clamp was applied every 15 minutes for a total time of 90 minutes and isoflurane administration was adjusted according to the response. Data were recorded at 30, 60 and 90 minutes for end-tidal isoflurane concentration (F_EIso), end-tidal carbon dioxide partial pressure ($P_E CO_2$), inspired isoflurane concentration (FIIso), arterial hemoglobin oxygen saturation (SaO_2), peripheral hemoglobin oxygen saturation (SpO_2), respiratory rate (f_R), heart rate (HR), arterial blood pH, $PaCO_2$, PaO_2, base excess (BE), bicarbonate (HCO_3^-), systemic arterial pressure (sAP), and biochemical variables of blood urea nitrogen, alanine aminotransferase, creatine kinase and creatinine.

Results No significant differences between treatments were detected for HR, f_R, SaO_2 or any biochemical variables ($p > 0.05$). In the Iso-nano treatment, sAP was significantly decreased throughout the study. Significant decreases in pH, $P_E CO_2$, BE and HCO_3^- were measured in the Iso-nano treatment. Isoflurane MAC was significantly lower in the Iso-nano than the Iso-I treatment. The dose of isoflurane (g hour^{-1}) required to maintain general anesthesia did not differ significantly between treatments.

Conclusions and clinical relevance Administration of 15% isoflurane-loaded lipid nanoemulsion IV was effective in maintaining general anesthesia in dogs but did not reduce the amount of isoflurane necessary to maintain general anesthesia. Significant hypotension and nonrespiratory acidosis occurred with the injectable form.

Keywords acid-base, halogenated anesthetics, isoflurane, nanoemulsion, nanotechnology.

Introduction

Isoflurane has been used frequently as an inhalant anesthetic in humans and animals because of its physical and chemical properties, such as low blood gas partition coefficient, and it does not cause cardiac arrhythmogenic effects (Steffey & Howland 1977; Ludders 1992; Eger 2005). Approximately 0.2% of inhaled isoflurane is metabolized in humans by the cytochrome 450 2E1 enzyme, which mediates reactions to acyl chloride, carbon dioxide,

Please cite this article in press as: Natalini CC, Krahn CL, Serpa PBS et al. Intravenous 15% isoflurane lipid nanoemulsion for general anesthesia in dogs, Veterinary Anaesthesia and Analgesia (2017), http://dx.doi.org/10.1016/j.vaa.2016.02.004

trifluoroacetic acid, fluoride ions and water (Eger 2005). Inorganic fluoride concentrations can be detected in the urine and blood of humans after isoflurane has been administered by inhalation (Holaday et al. 1975; Bradshaw & Ivanetich 1984; Preckel & Bolten 2005). The cytochrome 450 2E1 metabolic pathway is not present in rats (Bradshaw & Ivanetich 1984), which precludes the use of this species as a model in injectable isoflurane-loaded emulsions efficacy and safety studies.

There is growing interest in the intravenous (IV) use of halogenated anesthetics, and the IV route of administration has been studied in rats, mice, swine and dogs (Biber et al. 1984; Eger & MacLeod 1995; Musser et al. 1999; Krahn et al. 2012). Emulsification of inhalation anesthetics may reduce the time required to achieve equilibrium in brain and tissues, establishing the anesthetic state more consistently and faster than administration through the lungs (Eger & MacLeod 1995). Furthermore, it has been suggested that the amount of anesthetic drug necessary to establish anesthesia may be significantly reduced, which may potentially decrease both the incidence of side effects and costs (Krahn et al. 2012). In one published study in swine, the minimum alveolar concentration (MAC) for emulsified halothane was significantly reduced in comparison with that for inhaled halothane (Musser et al. 1999). A recent report indicated that 8% v/v lipid emulsified sevoflurane used to maintain general anesthesia in dogs did not reduce the amount of anesthetic needed for 120 minutes of anesthesia in comparison with inhaled sevoflurane (Natalini et al. 2016).

Halogenated anesthetics are limited to concentrations of 3.5–8.0% v/v when emulsified with a lipid (Zhou et al. 2006; Fast et al. 2008). Intralipid, a commercial lipid emulsion, is the vehicle often used for parenteral administration of isoflurane (Fast et al. 2008). However, this emulsion shows limited stability and hence phase separation can be observed within 24 hours of isoflurane incorporation. Lipid nanoemulsified inhaled anesthetics could potentially overcome both of these limitations, allowing a formulation with a higher concentration and more stability (Fast et al. 2008).

Emulsified halogenated anesthetics may be administered IV, intrathecally, epidurally, subcutaneously or intraperitoneally (Lucchinetti et al. 2008; Zhou & Liu 2012), which increases their versatility. Elimination of a halogenated anesthetic emulsion administered IV occurs primarily through the lungs (Eger & MacLeod 1995). In theory, pulmonary elimination should minimize deleterious effects that may occur as a result of metabolism.

In this study, we aimed to evaluate the effects of an injectable 15% isoflurane-loaded lipid nanoemulsion on cardiovascular variables, acid-base balance, and some indicators of renal and hepatic function in dogs, as well as the isoflurane consumption in g hour^{-1}.

Materials and methods

Approval was obtained from the Institutional Animal Care and Use Committee of the Clinical Hospital of Porto Alegre (RS, Brazil) (CEUA/HCPA, protocol no. 09-208).

Anesthetic agents and reagents

Reagents used included isoflurane 8.1 M (1.5 g mL^{-1}) (CAS: 26675-46-7; Cristália Produtos Químicos e Farmacêuticos Ltda, SP, Brazil) and medium chain triglycerides (Brasquim Indústria Química Importação Ltda, RS, Brazil), polysorbate 80 (Importadora Química Delaware Ltda, RS, Brazil), and sorbitol 70% (Sorbitol USP grade; ALZ Laboratórios Ltda, RS, Brazil). Soybean lecithin (Lipoid S75) containing 69.9% phosphatidylcholine, 8.4% phosphatidylethanolamine and 2.2% lysophosphatidylcholine was donated by Lipoid GmbH (Germany). Purified water was prepared using a Milli-Q Plus system (EMD Millipore, MA, USA).

Nanoemulsion preparation

A 15% isoflurane lipid nanoemulsion was prepared as described previously (Krahn et al. 2012). Lipoid S75 (1%) was dissolved in medium-chain triglycerides (15 mL) at 30 °C under magnetic stirring (Fisatom 753A; Scientific Equipments Ltda, SP, Brazil), after which the solution was cooled to 18 °C and isoflurane (15 mL) was added just before emulsification. The aqueous phase containing polysorbate 80 (2%), sorbitol (2.5%) and water (64.5 mL) was prepared under magnetic stirring at 30 °C (Fisatom 753A; Scientific Equipments Ltda) and cooled to 18 °C before emulsification. The oily phase was poured into the aqueous phase and emulsified in a high-shear mixer (Ultra-Turrax; Ika Labortechnik, Germany) at 16,000 ***g*** for 1 minute. The emulsion was then homogenized at high pressure (Panda 2K GEA; GEA Niro Soavi SpA, Italy) using the output cooler at 10 °C.

Study design

Seven healthy, mature, mixed-breed dogs, four males and three females, with a mean ± standard deviation

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