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RESEARCH PAPER

Effects of a prolonged infusion of fentanyl, with or without atropine, on the minimum alveolar concentration of isoflurane in dogs

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Abstract

Objectives To evaluate the effect of a prolonged constant rate infusion (CRI) of fentanyl on the minimum alveolar concentration (MAC) of isoflurane (ISO_{MAC}) and to establish whether concurrent atropine administration influences ISO_{MAC} in dogs.

Study design Prospective, crossover study.

Animals Six healthy dogs weighing 13.0 ± 4.1 kg.

Methods Dogs were anesthetized with isoflurane under conditions of normocapnia and normothermia. Arterial blood pressure was monitored invasively. Each dog was administered two treatments, on different occasions, in a crossover design. The dogs were administered intravenously (IV) an atropine bolus 0.02 mg kg^{-1} and CRI at 0.04 mg kg^{-1} $hour^{-1}$ (fentanyl–atropine treatment) or no atropine (fentanyl treatment). For each dog, baseline ISO_{MAC} was measured in duplicate using a tail clamp technique. Subsequently, all dogs were administered a fentanyl bolus (5 μg kg^{-1}) and CRI (9 μg kg^{-1} $hour^{-1}$) IV, and ISO_{MAC} was redetermined at 120 and 300 minutes after initiation of the fentanyl CRI.

Results Baseline ISO_{MAC} values in the fentanyl and fentanyl–atropine treatments were 1.38 ± 0.16% and 1.39 ± 0.14%, respectively. Fentanyl significantly decreased the ISO_{MAC} by 50 ± 9% and 47 ± 13% after 120 minutes and by 51 ± 14% and 50 ± 9% after 300 minutes ($p < 0.001$) in the fentanyl and fentanyl–atropine treatments, respectively. Compared with baseline, heart rate decreased significantly in the fentanyl treatment by 35% and 43% at 120 and 300 minutes, respectively. In the fentanyl–atropine treatment, heart rate did not change significantly over time. In both treatments, systolic arterial pressure increased from baseline after fentanyl.

Conclusions and clinical relevance In this study, fentanyl reduced the ISO_{MAC} by approximately 50%. The ISO_{MAC} remained stable throughout the 300 minute CRI of fentanyl, suggesting no cumulative effect of the opioid. Atropine did not influence ISO_{MAC} in dogs.

Keywords anticholinergic, inhalation anesthesia, opioid, phenylpiperidine derivative.

Introduction

Opioid analgesic drugs are administered during the intraoperative period with the aim of reducing requirements for inhalation anesthetic agents and blunting neuroendocrine responses to noxious stimulation (Mastrocinque & Fantoni 2003; Allweiler

et al. 2007; Bufalari et al. 2007). Numerous studies have shown that μ-opioid agonists decrease the minimum alveolar concentration (MAC) of inhalation anesthetics in a dose-dependent manner in dogs (Murphy & Hug 1982; Hellyer et al. 2001; Ueyama et al. 2009).

Fentanyl is a synthetic opioid with high affinity for μ-receptors. It has a rapid onset of action after intravenous (IV) administration, which supports its intraoperative use for the provision of surgical analgesia (Pascoe 2000). Fentanyl has a short distribution half-time of approximately 3 minutes in dogs and 99% of a single dose (10 μg kg^{-1}) has been shown to disappear from the plasma within 30 minutes after IV administration in dogs (Murphy et al. 1979). The effects of fentanyl have been found to correlate with plasma concentrations (Murphy & Hug 1982). Consequently, prolongation of analgesia by administration of fentanyl as a constant rate infusion (CRI) has been proposed (Pascoe 2000; Lamont & Mathews 2007). Administration of a fentanyl CRI can reduce the MAC of enflurane by up to 65% (Murphy & Hug 1982).

The context-sensitive half-time is defined as the time to a 50% decrease in the plasma concentration of a drug after the infusion is discontinued (Bürkle et al. 1996). It has been proposed as a more accurate prediction of recovery from IV infusion of an anesthetic agent than the terminal elimination half-life (Kapila et al. 1995). In humans, the context-sensitive half-time of fentanyl was found to depend on the duration of infusion and a rapid rise in plasma concentration was observed during a CRI of > 3 hours (Hughes et al. 1992). Available pharmacokinetic data for fentanyl administered as a CRI in dogs differ from those reported in humans. In one study, the plasma concentration of fentanyl remained relatively stable in conscious dogs during a 4 hour CRI at 10 μg kg^{-1} $hour^{-1}$ (Sano et al. 2006).

Concurrent administration of an inhalation anesthetic may influence the pharmacokinetics of fentanyl (Sano et al. 2006). In enflurane-anesthetized dogs, IV administration of three successive doses of fentanyl (10 μg kg^{-1} each) resulted in accumulation as indicated by progressively higher plasma concentrations of the opioid (Murphy et al. 1979). Furthermore, the reduction in MAC of enflurane by fentanyl was found to depend on the plasma concentration of the opioid (Murphy & Hug 1982). Thus it might be speculated that, if accumulation occurs during a prolonged infusion of fentanyl, a rise in its plasma concentration will result in a greater sparing effect on the MAC over time. To the authors' knowledge, no study has reported the effects of a prolonged infusion of fentanyl on the MAC of inhalation anesthetic agents in dogs.

Bradycardia is the cardiovascular effect of an opioid of most concern (Lamont & Mathews 2007). A reduction of approximately 50% in heart rate (HR) has been reported in enflurane-anesthetized dogs administered a fentanyl CRI (Ilkiw et al. 1994). Anticholinergic agents are used to prevent or to treat opioid-induced bradycardia (Lamont & Mathews 2007). In studies on the determination of MAC, glycopyrrolate has been preferred over atropine for this purpose because it does not cross the blood–brain barrier in dogs (Proakis & Harris 1978) and is less likely to influence MAC. Although intramuscular (IM) administration of atropine (0.045 mg kg^{-1}) did not influence the MAC of halothane in cats (Webb & McMurphy 1987), its effect on the MAC of inhalation anesthetics has not been determined in dogs.

The primary objective of the present study was to evaluate the effect of a prolonged CRI of fentanyl on the MAC of isoflurane (ISO_{MAC}) in dogs. We hypothesized that the ISO_{MAC} determined at 300 minutes after initiation of a fentanyl CRI would be decreased to a greater extent than the ISO_{MAC} determined at 120 minutes after the start of the CRI. This study also investigated the effect of a CRI of atropine on the ISO_{MAC}.

Materials and methods

Animals

This study was approved by the Institutional Animal Care Committee of the University of Vila Velha, Vila Velha, ES, Brazil (protocol 178/2011). Six adult spayed female mongrel dogs weighing 13.0 ± 4.1 kg were used. Health status was assessed by means of physical examination, an electrocardiogram (ECG), a complete blood count and serum chemistry measurements. Any dog with clinical signs of systemic disease or abnormal laboratory data was excluded from the study.

Instrumentation

Food but not water was withheld for 12 hours prior to anesthesia. A 20 gauge catheter (BD Angiocath; Becton, Dickinson & Co., SP, Brazil) was placed in a