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RESEARCH PAPER

Effects of acepromazine or dexmedetomidine on fentanyl disposition in dogs during recovery from isoflurane anesthesia

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Abstract

Objective To describe fentanyl pharmacokinetics during isoflurane anesthesia and on recovery from anesthesia with concurrent administration of acepromazine, dexmedetomidine or saline in dogs.

Study design Experimental blinded, randomized, crossover study.

Animals Seven adult hound dogs.

Methods Dogs were administered intravenous (IV) fentanyl as a bolus (5 μg kg^{-1}) followed by an infusion (5 μg kg^{-1} $hour^{-1}$) for 120 minutes during isoflurane anesthesia and emergence from anesthesia, and for 60 minutes after extubation during recovery from anesthesia. At the time of extubation, dexmedetomidine (2.5 μg kg^{-1}), acepromazine (0.05 mg kg^{-1}) or saline were administered IV. Venous blood was sampled during the maintenance and recovery periods. Fentanyl plasma concentrations were measured using high-performance liquid chromatography–mass spectrometry and population pharmacokinetic analyses were performed.

Results Mean fentanyl plasma concentrations were 1.6–4.5 ng mL^{-1} during isoflurane anesthesia and 1.6–2.0 ng mL^{-1} during recovery from anesthesia. Recovery from isoflurane anesthesia without sedation was associated with an increase in the volume of the central compartment from 0.80 to 1.02 L kg^{-1}. After administration of acepromazine, systemic clearance of fentanyl increased from 31.5 to 40.3 mL $minute^{-1}$ kg^{-1} and the volume of the central compartment increased from 0.70 to 0.94 L kg^{-1}. Administration of dexmedetomidine did not significantly change fentanyl pharmacokinetics. Inter-individual variability for fentanyl parameter estimates in all treatments ranged from 2.2% to 54.5%, and residual error ranged from 6.3% to 13.4%.

Conclusions and clinical relevance The dose rates of fentanyl used in this study achieved previously established analgesic plasma concentrations for the duration of the infusion. Despite alterations in fentanyl pharmacokinetics, differences in fentanyl plasma concentrations among treatments during recovery from anesthesia were small and were unlikely to be of clinical significance.

Keywords acepromazine, anesthesia, dexmedetomidine, dog, fentanyl, recovery.

Introduction

Opioids are routinely administered to dogs to provide analgesia during the intraoperative and postoperative periods (Steagall et al. 2006; Egger et al. 2007). Short-acting opioids are frequently delivered as intravenous (IV) infusions, following a loading dose, to minimize fluctuations in plasma drug concentrations that would occur with repeated bolus administration, and to provide consistent and titratable analgesia (Sano et al. 2006; Anderson & Day 2008). Fentanyl is a synthetic μ-opioid receptor agonist with a rapid onset and short duration of action. It is often used as an IV infusion in dogs intraoperatively to reduce requirements for other anesthetic agents and to improve analgesia, and administration is continued into the period of recovery from anesthesia in order to manage postoperative pain (Ilkiw et al. 1994; Steagall et al. 2006; Anderson & Day 2008).

Dogs may also be administered a sedative with an opioid during recovery from anesthesia with the aim of preventing or minimizing dysphoria caused by opioid administration, emergence delirium or general anxiety (Dyson et al. 1998). Acepromazine and dexmedetomidine have been recommended for this purpose (Pascoe 2000). Although both drugs provide sedation in dogs during recovery from anesthesia, their combination with an opioid can result in additive or synergistic cardiopulmonary depression (Jacobson et al. 1994; Grimm et al. 2005; Monteiro et al. 2008). It is currently unknown whether the physiologic effects resulting from these drug interactions are caused by pharmacodynamic alterations alone, or whether pharmacokinetic interactions also play a role.

The pharmacokinetics of fentanyl following an IV loading dose and constant rate infusion (CRI) have been previously evaluated in conscious dogs (Sano et al. 2006); however, pharmacokinetic analysis of a fentanyl CRI has not been performed in dogs anesthetized with isoflurane. Inhalation anesthetics have been shown to significantly alter the pharmacokinetic profiles of fentanyl, lidocaine and remifentanil in other species (Feary et al. 2005; Thomasy et al. 2005, 2007; Pypendop et al. 2008). Dexmedetomidine may also be associated with significant drug interactions (Kharasch et al. 1991, 1992) and has been shown to increase alfentanil plasma concentrations in human patients (Karol & Maze 2000). Despite the potential for significant drug interactions, there are currently no published studies evaluating the effects of different sedatives on fentanyl pharmacokinetics. The objectives of the current study were: 1) to describe fentanyl pharmacokinetics in dogs under isoflurane anesthesia; 2) to characterize changes in fentanyl disposition resulting from the elimination of isoflurane and recovery from anesthesia; and 3) to determine the pharmacokinetic influences of concurrently administered acepromazine or dexmedetomidine.

Materials and methods

Animals

Seven intact, purpose-bred, male hounds were used in the study. Dogs were aged 11–12 months and had a mean ± standard deviation (SD) body weight of 22.3 ± 1.2 kg. They were considered to be healthy based on their history, physical examination, complete blood count and serum biochemistry analyses. All dogs were allowed free access to water, but food was withdrawn for 12 hours prior to induction of anesthesia. The study was approved by the Institutional Animal Care Committee at the University of Guelph (ON, Canada).

Experimental design

A randomized, blinded, crossover design was used to evaluate fentanyl pharmacokinetics in three treatments. The treatment order was randomized manually for each dog by the blind drawing of a series of papers containing the treatment codes. Each dog was submitted to the same protocol for the induction and maintenance of anesthesia before the administration of the treatment drug at the time of recovery from anesthesia. Dogs underwent a washout period of at least 7 days between treatments.

Study protocol

The study protocol has been described previously in detail (Keating 2013; Keating et al. 2013). Anesthesia was induced with propofol (Diprivan 1%; AstraZeneca Canada, Inc., ON, Canada) IV to effect (5.7 ± 0.5 mg kg^{-1}) and, after endotracheal intubation, was maintained with isoflurane (IsoFlo; Abbott Laboratories Ltd, QC, Canada) delivered in