Veterinary Anaesthesia and Analgesia 2017, **xxx**, 1–9 http://dx.doi.org/10.1016/j.vaa.2016.05.010

RESEARCH PAPER

Pharmacokinetics of buprenorphine following constant rate infusion for postoperative analgesia in dogs undergoing ovariectomy

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Abstract

Objective To investigate the pharmacokinetics of buprenorphine and its main active metabolite, norbuprenorphine, after administration of an intravenous loading dose followed by constant rate infusion (CRI) in dogs.

Study design Prospective, clinical study.

Animals A total of seven healthy dogs undergoing elective ovariectomy.

Methods Buprenorphine was administered as a loading dose (intravenous bolus of 15 μg kg^{-1}) followed by CRI (2.5 μg kg^{-1} $hour^{-1}$ for 6 hours). Moreover, intraoperative analgesia was supplemented by an intramuscular carprofen (4 mg kg^{-1}) injection, given prior to surgery, and by lidocaine, administrated through subcutaneous infiltration and through a splash on the ovarian vascular pedicle during surgery. Pain and sedation were scored for all animals throughout the 24-hour study period and rescue analgesia was administered when a visual analogue scale was > 40 mm. Blood samples were collected from a jugular catheter at regular intervals, and plasma concentrations of buprenorphine and norbuprenorphine were determined by a validated liquid chromatography–tandem mass spectrometry method.

Results Buprenorphine showed a two-compartment kinetic profile. Maximum concentration was 23.92 ± 8.64 ng mL^{-1} at 1 minute (maximum time); elimination half-life was 41.87 ± 17.35 minutes; area under the curve was 486.68 ± 125.66 minutes ng mL^{-1}; clearance was 33.61 ± 13.01 mL $minute^{-1}$ kg^{-1}, and volume of distribution at steady state was 1.77 ± 0.50 L kg^{-1}. In no case was rescue analgesia required. Norbuprenorphine resulted below the lower limit of quantification in almost all samples.

Conclusions and clinical relevance The results suggest that a buprenorphine CRI can be a useful tool for providing analgesia in postoperative patients, considering its minor side effects and the advantages of a CRI compared to frequent boluses. The negligible contribution of norbuprenorphine to the therapeutic effect was confirmed.

Keywords buprenorphine, continuous rate infusion, dog, liquid chromatography–tandem mass spectrometry, pharmacokinetics.

Introduction

Numerous research papers from the 1990s highlighted the fact that analgesics were dramatically under-used in animals for the management of pain (Flaherty 2012). During the past two decades, awareness of both the deleterious effects of pain and its related ethical component have brought progress in pain recognition and management in veterinary medicine, and this trend is likely to continue. Opioids, as small animal analgesic agents, have historically been of great importance. Buprenorphine is a semi-synthetic, highly lipophilic derivate of the morphine alkaloid thebaine (Andaluz et al. 2009; Kelly et al. 2014) that is widely employed in small animals in Europe, South Africa, Australia and the USA (Krotscheck et al. 2008). Buprenorphine has an affinity to the opiate receptors that is twice as high and an analgesic effect which is about 30–40 times higher than morphine (Park et al. 2008). Despite

Please cite this article in press as: Barbarossa A, Rambaldi J, Giunti M et al. Pharmacokinetics of buprenorphine following constant rate infusion for postoperative analgesia in dogs undergoing ovariectomy, Veterinary Anaesthesia and Analgesia (2017), http://dx.doi.org/10.1016/j.vaa.2016.05.010

earlier misconceptions, buprenorphine has been shown to act as a full μ-agonist analgesic with no ceiling effect for pain. Unlike other opioids, it exhibits a ceiling effect for respiratory depression, acting as a partial agonist for this end point (Yassen et al. 2008; Pergolizzi et al. 2010; Raffa et al. 2014). The combination of long duration of action, low risk of respiratory depression, and negligible cardiovascular effects in healthy dogs make buprenorphine an advantageous opioid analgesic agent for use with procedures associated with mild to moderate pain (Nunamaker et al. 2014).

In dogs, buprenorphine is successful in managing postoperative pain through different administration routes, including intravenous (IV) (Morgaz et al. 2013), intramuscular (IM) (Slingsby et al. 2011), transmucosal (Ko et al. 2011), subcutaneous, and transdermal (Moll et al. 2011). In canine clinical practice, it is usually administered 0.01−0.02 mg kg^{-1} IM or IV (single bolus), providing analgesia for 6−8 hours (Andaluz et al. 2009), although a recent study proposed a dosing interval of 4−6 hours (Slingsby et al. 2011).

Ovariectomy is one of the most commonly performed surgical procedures in small animals (Fox et al. 2000), and it is often used in research on analgesics because it is considered to cause predictable and repeatable abdominal postoperative pain (Capner et al. 1999; Coleman & Slingsby 2007). Buprenorphine is believed to be a good analgesic for this type of surgery in dogs (Nunamaker et al. 2014), although some authors suggest that it might provide a superior analgesic effect if administered in combination with nonsteroidal anti-inflammatory drugs, especially in the preoperative phase (Lascelles et al. 1998; Lamont 2008; Shih et al. 2008). The slow and continuous drug delivery over a long period, as provided by constant rate infusion (CRI) or transdermal patches, improves the quality of analgesia, reducing concentration peaks, frequency of dosing and drug toxicity. It also avoids the hepatic first-pass metabolism associated with opioid oral administration (Murrell et al. 2007). Recently, transdermal patches have been developed to optimize opiate delivery (Park et al. 2008; Yassen et al., 2008) and, to our knowledge, only one study has been conducted on buprenorphine CRI pharmacokinetics (PK) in dogs, using suprapharmacologic doses (IV infusion in the 3.7−4.8 mg kg^{-1} range over 3 hours), thus limiting the applicability of these data to clinical use (Garret and Chandran 1990).

In light of the above, the purpose of the present study was to evaluate the PK of buprenorphine and its active metabolite, norbuprenorphine, in dogs following a combined bolus-CRI IV administration, in order to establish the effect of this dosing regimen and to report any potential adverse effects.

Materials and methods

Animals

All procedures performed in this study were approved by the Ethics Committee of the University of Bologna and then by the Italian Ministry of Health on 1st December 2010 (Prot. N. 55948-X/10). The approval was obtained for eight healthy dogs.

Around 90 dogs were referred to the Veterinary Teaching Hospital for elective ovariectomy during a 6-month period, between September 2011 and February 2012. Inclusion criteria were female mixed-breed dogs that were nonaggressive, aged between 8 months and 6 years and weighing > 12 kg. Their health status was evaluated on the basis of medical history, physical examination, and haematological and biochemical analyses and only those classified as I according to the American Society of Anesthesiology were included. The reproductive tract was assessed by physical examination and ultrasound evaluation, and only animals without any evident disorder were included. Dogs had to be in anoestrus, confirmed by the absence of oestrous clinical signs, vaginal cytology, and serum progesterone concentration. Eight client-owned dogs were randomly enrolled in the study. A die was rolled for each admitted dog meeting the inclusion criteria and, having informed client consent, those with an even number were included and those with an odd number excluded, until the approved number was reached.

Study design

The animals were fasted for 8 hours before surgery, with *ad libitum* access to water until sedation. Baseline physiological measurements [heart rate (HR), respiratory rate (f_R), temperature (T)] were recorded. All dogs were premedicated with IM administration of 20 μg kg^{-1} of acepromazine maleate (Prequillan; ATI, Italy) and 4 mg kg^{-1} of carprofen (Rimadyl; Zoetis, Italy).

After 15 minutes, an IV catheter was placed into a cephalic vein for anaesthesia induction. The animals were then prepared for surgery: the neck in the area

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