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Comparison of a new metamizole formulation and carprofen for extended post-operative analgesia in dogs undergoing ovariohysterectomy

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ABSTRACT

A newly developed slow-release tablet formulation of metamizole was compared with carprofen for post-operative analgesia in dogs undergoing ovariohysterectomy. Twenty-three dogs were randomly assigned to one of two groups, and administered 50 mg/kg metamizole PO (Group M) or 4 mg/kg carprofen PO (Group C) 1 h before anaesthetic induction and 24 and 48 h later. Anaesthesia was induced with propofol and maintained with isoflurane and fentanyl, after premedication with 0.005 mg/kg medetomidine and 0.3 mg/kg methadone IM. A blinded observer assessed post-operative sedation, and analgesia using a visual analogue scale, a dynamic interactive visual analogue scale, the Glasgow composite pain scale (GCPS), and a mechanical nociceptive threshold device (T = 0.5, 1, 2, 4, 8, 12, 18, 21, 24, 36, 45, 60 and 70 h after surgery). Rescue methadone was administered if the GCPS was >6/24 in ambulatory dogs, or >5/20 in non-ambulatory dogs. Plasma concentrations of test drugs were quantified.

The dose range for metamizole was 39–56 mg/kg. At T = 0.5 h sedation scores were significantly higher in Group C and GCPS scores were significantly higher in Group M. Three dogs required rescue methadone (Group M, $n = 1$; Group C, $n = 2$). Vomiting occurred post-operatively in 45% of dogs in Group M. Carprofen and metamizole were both well absorbed; peak concentrations occurred within 4–24 h, and 4–16 h for carprofen and metamizole, respectively. Both drugs provided adequate analgesia of similar duration. No side effects were observed with carprofen while vomiting was frequent following administration of metamizole.

Introduction

Oral medication is the preferred method for extended post-operative pain control for 'day-case' procedures such as ovariohysterectomy (OHE) as the drug can be administered by owners. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for this purpose, although these can lead to a variety of side effects including gastrointestinal, renal, and haemostatic disorders (Curry et al., 2005; Luna et al., 2007; Monteiro-Steagall et al., 2013). Carprofen has been studied extensively in dogs in the perioperative (Nolan and Reid, 1993; Fox and Johnston, 1997; Lascelles et al., 1998; Laredo et al., 2004; Shih et al., 2008) and also in the extended post-operative period (Leece et al., 2005). An advantage of carprofen is that it is generally administered only once daily, thereby improving owner compliance (Pullar et al., 1988; Barter et al., 1996).

Metamizole, a pirazolone derivative also known as dipyrone, is an atypical NSAID, which has been on the market for more than 90 years. Metamizole is an antipyretic analgesic with spasmodic properties and lacks anti-inflammatory activity (Levy et al., 1995; Camu and Vanlersberghe, 2002). Although banned in some countries (including USA and the Scandinavian countries) in the 1980s due to the rare but serious occurrence of agranulocytosis as a side effect (Hedenmalm and Spigset, 2002), it is still widely used in several European and South American countries. There are no reports of agranulocytosis in veterinary medicine.

In the last few years, metamizole has experienced a revival, especially for pain management in human medicine, due to its high efficacy and good gastric tolerability (Sanchez et al., 2002; Nikolova et al., 2013). Peripheral as well as central effects are responsible for the potent analgesic efficacy (Mazario and Herrero, 1999; Vazquez et al., 2007). Opioidergic pathways (Tortorici et al., 1996) and

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inhibition of cyclooxygenase (COX)-3 (Chandrasekharan et al., 2002) seem to be the main mechanisms of action; the analgesic effect is comparable to that of opioids in humans (Hempel, 1986; Aguirre-Banuelos and Granados-Soto, 1999) and dogs (Richter et al., 2007; Tacke et al., 2008). Metamizole has been shown to be effective in controlling post-operative pain in dogs undergoing OHE (Imagawa et al., 2011).

Until now metamizole was approved for the veterinary market only as an injectable formulation, whereas for many years tablets for humans have been licensed with a duration of action of 4–6 h (Brack and Schäfer, 2008). To enable drug administration by pet owners an oral formulation for dogs was needed, and to increase owner compliance one with a longer duration of action in dogs was developed. A polymer, povidone, was used for controlling the drug release; in an aqueous environment the polymer in the tablet swells and forms a gel. Metamizole sodium dissolves in the gel and diffuses out into the surroundings.

The aim of the present study was to compare the efficacy and duration of analgesia of a new slow-release formulation of metamizole with those of the classic NSAID carprofen in dogs for 70 h after undergoing OHE surgery, and to measure the plasma concentrations.

Materials and methods

This blinded, randomized study was approved by the Committee for Animal Experimentation of Canton Zurich, Switzerland (182/2009).

Twenty-three female client-owned dogs, weighing ≥5 kg, aged ≥6 months, were recruited to the study; written owner consent was provided. Further inclusion criteria were (1) a healthy clinical condition on physical examination and blood work (haematology and chemistry), and (2) non-aggressive, cooperative behaviour. One blinded observer (RW) performed scoring of pain and sedation in all dogs; one blinded anaesthetist (AS) performed all anaesthetics; the only unblinded person involved was the 'dispenser', who administered the study drugs but was otherwise not related to the study.

Dogs arrived at the surgical facilities on the morning before surgery for preoperative evaluation and familiarisation with the study setting. Dogs were fasted for 8 h prior to anaesthesia. Access to water was permitted until administration of the premedication. Two hours before induction of anaesthesia, baseline measurements were collected for heart rate (HR), respiratory rate (*fr*), and rectal temperature (T), and mechanical nociceptive threshold (MNT) in close proximity to the planned incision line. Baseline assessments of sedation and pain were also performed (see below). One hour prior to induction of anaesthesia the study medication was administered by the dispenser.

The dogs were randomly assigned into two groups. Those in group M received 50 mg/kg metamizole PO (R&D-CFT Formulation, Bayer Animal Health), and those in group C received 4 mg/kg carprofen PO (Rimadyl, Pfizer). The same medication was repeated 24 h and 48 h later. The metamizole tablets were based on a preliminary formulation (500 mg) and could not be halved, resulting in a variation in the dose of metamizole between 39 and 56 mg/kg. Thirty minutes later the dogs were sedated with 0.005 mg/kg medetomidine (Domitor, Pfizer) and 0.3 mg/kg methadone IM (Methadon Streuli, Streuli Pharma). After a further 30 min, an IV catheter was placed in a cephalic vein after sterile preparation, and anaesthesia was induced with propofol IV (Propofol 1% MCT Fresenius, Fresenius Kabi) until conditions were adequate for orotracheal intubation.

After intubation the dogs were connected via a rebreathing system to the anaesthetic machine (Megamed 700). All of the dogs were mechanically ventilated throughout anaesthesia to maintain end-tidal carbon dioxide partial pressure ($PE'CO_2$) between 35 and 45 mmHg. Anaesthesia was maintained with isoflurane (Isoflo, Abbott) in oxygen and air (inspiratory oxygen concentration 0.4–0.5) and a continuous rate infusion (CRI) of fentanyl (Sintenyl, Sintetica). Fentanyl CRI was started at 5 μg/kg/h; this was adjusted every 5 min according to HR and mean arterial blood pressure (MAP): increase in HR and/or mean MAP > 10%: +5 μg/kg/h; decrease in HR and/or MAP > 10%: −5 μg/kg/h. The total dose of fentanyl administered was recorded. All dogs received 10 mL/kg/h lactated Ringer's solution during surgery and 22 mg/kg cephazolin IV once.

After aseptic preparation of the surgical field, one experienced surgeon (SF) performed OHE via midline coeliotomy in all dogs. HR, *fr*, oscillometric blood pressure, haemoglobin saturation with oxygen (SpO_2), $PE'CO_2$, and inspired and expired isoflurane concentration were continuously monitored (Cardiocap/5, Anandic) and recorded every 5 min. The duration of surgery was recorded. Anaesthesia duration was standardized at 120 min.

Post-operative measurements

After the end of anaesthesia (disconnection from breathing system = T0), the dogs were transported to the ward for recovery. The time of extubation was recorded. Post-operative measurements and assessments were performed at times (T) 0.5, T1, T2, T4, T8, T12, T18, T21, T24, T36, T45, T60, and T70 h by the same blinded observer (RW). Vital parameters (HR, *fr*, body temperature, capillary refill time and colour of mucous membranes) were assessed at the same time points.

Sedation was assessed using a scale from 0 to 3 points as follows: dog is completely awake, can walk (0); dog is slightly sedated, can lift head (1); dog is heavily sedated, reacts upon vocal interaction (2); dog sleeps, does not react upon vocal stimulation (3).

Pain scoring was performed using four different methods. (1) A visual analogue scale (VAS) of 100 mm was used with the ends anchored at 0 = no pain and 100 = worst possible pain after OHE, not including any interaction with the observer. (2) The short form of the Glasgow composite pain scale (GCPS; Reid et al., 2007)[1] was used with a possible maximum of 24 points, or 20 if mobility is impossible to assess. (3) Measurement of wound sensitivity was measured using a mechanical nociceptive threshold (MNT) measuring device; this was tested using a pen-like force gauge with a rounded metal probe with a pen diameter of 4 mm, head radius of 2 mm and resultant contact surface of 25 mm^2 (SMALGO, Bioseb).[2] Steadily increasing pressure was applied in close proximity (10 mm) to the incision line until the animal showed a response. Any sudden movement of the dog away from the device, turning of the head towards the device, vocalisation, a sudden tense abdomen, or attempts to bite were considered a response. Pressure was then instantly released and the applied force in Newtons (N) was read from the display; three measurements were taken at each time point and the highest preoperative measurement (baseline) was taken as the individual limit not to be exceeded when performing post-operative measurements, with an overall limit of 13 N. The average of the three measurements was recorded as MNT value for statistical analysis. (4) A dynamic interactive analogue scale (DIVAS) was used, similar to the VAS on a scale of 100 mm, but incorporating the interaction with the observer (Lascelles et al., 1998).

All measurements and assessments were always performed in the same order, with increasing invasiveness. Rescue analgesia with 0.3 mg/kg methadone IM was administered if >6/24 or 5/20 points were reached in the GCPS. Any complications were noted.

Blood samples and analysis

Venous blood samples (4 mL) were obtained from the jugular vein prior to test drug application (baseline) and 4, 6, 12, 16, 20 and 24 h after the first administration. Plasma was separated by centrifugation within 1 h and stored at –80 °C. To obtain samples from the cephalic catheter in the post-operative period, 2 mL of blood was first discarded. If it was technically not possible to draw a blood sample from the IV catheter, it was taken from the jugular vein.

Analysis of the blood samples was performed by Bayer Crop Science. As metamizole is rapidly hydrolysed, the active metabolites 4-methyl-amino-antipyrine (MAA) and 4-amino-antipyrine (AA) were determined by high performance liquid chromatography (HPLC) and tandem mass spectrometry; metamizole concentrations were calculated from the concentrations of the metabolites ([AA]1.532 + [MAA]1.433; Bayer Crop Science Development). Plasma levels of carprofen were similarly measured. Levels of quantification were 0.025 μg/mL. Relative standard deviations were 3.6% for the determination of MAA, 4.5% for AA, and 6.5% for carprofen.

Final examination

After termination of the study dogs underwent another physical examination, and a venous blood sample was taken for measurement of hepatic and renal parameters (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), urea, and creatinine).

Statistical analysis

Data were assessed using the Wilks–Shapiro normality test and appropriate statistical techniques for parametric (age, weight, vital parameters) and non-parametric data were applied (NCSS 2007 Version 07.1.20). For analysis of parametric data a two-tailed *t* test was used; non-parametric Wilcoxon-Rank-Sum Tests (or Mann–Whitney *U* Tests) were used to assess the presence of differences in medians. Fisher's exact test was used to compare the need for rescue analgesia, as well as the occurrence of salivation and vomiting between groups. *P* values <0.05 were considered to be significant. Data are presented as means ± SD for parametric data and as medians ± interquartile range (IQR) for non-parametric data.

[1] See: http://www.gla.ac.uk/media/media_233876_en.pdf.

[2] As modified by Dr Thomas Wiestner, University of Zurich (Kalchofner Guerrero et al., 2014).