Veterinary
Anaesthesia and Analgesia
Formerly the Journal of Veterinary Anaesthesia

Veterinary Anaesthesia and Analgesia, 2014 doi:10.1111/vaa.12235

RESEARCH PAPER

Pharmacokinetic profiles of the analgesic flupirtine in dogs after the administration of four pharmaceutical formulations

Virginia De Vito*, Beata Łebkowska-Wieruszewska†, Ahmed Shaban‡, Andrzej Lisowski§, Cezary J Kowaski† & Mario Giorgi*

*Department of Veterinary Sciences, University of Pisa, San Piero a Grado, Italy

†Department of Pharmacology, University of Life Sciences, Lublin, Poland

‡Department of Pharmacology, University of Zagazig, Zagazig, Egypt

§Department of Animal Hygiene and Environment, University of Life Sciences, Lublin, Poland

Correspondence: Mario Giorgi, Department of Veterinary Sciences, University of Pisa, 56122 San Piero a Grado, Italy.
E-mail: mgiorgi@vet.unipi.it

Abstract

Objective Flupirtine (FLU) is a non-opioid analgesic with no antipyretic or anti-inflammatory effects which is used in the treatment of pain in humans. There is a substantial body of evidence on the efficacy of FLU in humans but this is inadequate for the recommendation of its off-label use in veterinary clinical practice. The aim of this study was to evaluate the pharmacokinetic profiles of FLU after intravenous (IV), oral immediate release (POIR), oral prolonged release (POPR) and rectal (RC) administrations in healthy dogs.

Study design Four-treatment, single-dose, four-phase, unpaired, cross-over design (4 × 4 Latin-square).

Animals Six adult Labrador dogs.

Methods Animals in groups 1, 2 and 4 received a single dose of 5 mg kg^{-1} FLU administered by IV, POIR and RC routes. Group 3 received a single dose of 200 mg $subject^{-1}$ via the POPR route. The wash-out periods were 1 week. Blood samples (1 mL) were collected at assigned times for 48 hours and plasma FLU concentrations were analysed by a validated HPLC method.

Results Adverse effects including salivation, tremors and vomiting were noted in the IV group and resolved spontaneously within 10 minutes. These effects did not occur in the other groups. The FLU plasma concentrations were detectable in all of the treatment groups for 36 hours following administration. The pharmacokinetic profiles after extravascular administrations showed similar trends. The bioavailability values after POIR, POPR and RC were 41.93%, 36.78% and 29.43%, respectively. There were no significant differences in pharmacokinetic profiles between the POIR and POPR formulations. A 5 mg kg^{-1} POIR dose or a 200 mg $subject^{-1}$ POPR dose gave plasma concentrations similar to those reported in humans after clinical dosing.

Conclusion and clinical relevance This study provides pharmacokinetic data that can be used to design further studies to investigate FLU in dogs.

Keywords analgesic, biopharmaceutics, dogs, flupirtine, pharmacokinetics.

Introduction

Companion animals are living longer and so are suffering from more age-related diseases that can be associated with pain such as cancer, arthritis and

metabolic disorders (Giorgi 2012a). Attentive and effective pain management in dogs facilitates recovery from painful conditions and a quicker return to physiological normality (Lamont 2008). The most popular analgesics licensed for dogs include nonsteroidal anti-inflammatory drugs and opioids (KuKanich 2013). The small number of drugs approved for dogs has been the impetus for the recent movement towards the development of more effective and innovative veterinary therapies (Giorgi & Yun 2012; Giorgi et al. 2012). An increasingly popular solution to the limited range of analgesics for dogs has been off-label drug use (Giorgi 2012b; Giorgi & Owen 2012b) but it is not prudent to extrapolate the use of drugs in one species to another. Pharmacokinetic and pharmacodynamic studies in the target species are important.

Flupirtine (FLU) is one compound which has been suggested as having potential for use in veterinary medicine (Giorgi & Owen 2012a). It is an aminopyridine drug (ethyl {2-amino-6-[(4-fluorobenzyl) amino]pyridin-3-yl}carbamate) that was first approved in Europe in 1984 for the treatment of pain in humans (Kumar et al. 2013). FLU is a centrally acting analgesic with a mechanism of action unlike that of opiates. It has no antipyretic or anti-inflammatory effects and is well tolerated (Singal et al. 2012). It is the first drug to be recognised in the unique class of 'Selective Neuronal Potassium Channel Openers' (SNEPCO) (Kornhuber et al. 1999). FLU interacts with the G-protein-regulated, Inwardly Rectifying K^+ channels (GIRKs), a novel family of K^+ channels that are distinct from voltage-dependent K^+ channels. They are regulated by neurotransmitters and are expressed in different parts of the brain. FLU activates GIRKs and stabilizes the resting membrane potential by activating KCNQ potassium channels and thus generating a neuronal hyperpolarizing current (M-current). The increased M-current due to the action of FLU decreases neuronal excitability (Kolosov et al. 2012). Moreover, FLU inhibits the NMDA receptor indirectly by acting as an oxidizing agent at the redox site of the NMDA receptor, maintaining the Mg^{2+} block on the NMDA receptor (Singal et al. 2012).

FLU can be useful in the treatment of a wide range of pain states in humans. In line with its mechanism of action promoting neuronal rest, it has proven useful in conditions involving neuronal hyperexcitability such as chronic pain (non-malignant and malignant), migraines and neurogenic pain (Luben et al. 1994; Wörz et al. 1996; Mueller-Schwefe 2003; Ringe et al. 2003; Li et al. 2008; Szelenyi 2013). Its muscle relaxant effects provide additional benefits in painful conditions associated with increased muscle tension, such as musculoskeletal back pain, myofascial pain and tension headaches (Wörz 1991; Wörz et al. 1995, 1996; Banerjee et al. 2012; Kumar et al. 2013). FLU has also been shown as beneficial in the short-term treatment of acute pain to pain of a moderate duration such as postoperative pain, trauma and dysmenorrhoea (Heusinger 1987). The approved indications of FLU differ between countries but mainly include the clinical management of the pain states mentioned above. It has possibly not been used to its full potential as an analgesic in the first decade of the 21st century. In recent years, there has been resurgence in FLU use after discovery of its powerful additive effects when used with opioids (Goodchild et al. 2008; Capuano et al. 2011; Kolosov et al. 2012) as well as its properties when used alone (Wilhelmi 2013).

There is a substantial body of evidence on the efficacy of FLU in humans however this is inadequate to recommend its off-label use in dogs in veterinary clinical practice (Giorgi & Owen 2012a). The aim of this study was to evaluate the pharmacokinetic profiles of FLU after intravenous (IV), oral immediate release (POIR), oral sustained release (POPR) and rectal (RC) administration in healthy dogs.

Materials and methods

Animals and experimental design

The animal experiment was approved by the animal welfare ethics committee of the University of Lublin (authorization # 62014) and carried out in accordance with the European law (EC council Directive 86/609 EEC). Six adult, intact Labradors, one male and five females, aged between 3 and 6 years, with a body mass in the range of 34–40 kg, were enrolled in the study. The dogs were determined to be clinically healthy based on physical examination and serum chemistry and haematological analyses. Animals were evaluated daily (up to 1 week after the completion of the study) for visible adverse effects by trained personnel. Two weeks after the end of the study the dogs underwent a health-check for physical and behavioural abnormalities.

Dogs were randomly assigned to four treatment groups (six slips of paper marked with the numbers 1 to 6 in a box), using an open, single-dose,

