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RESEARCH PAPER

Analgesic efficacy of an oral transmucosal spray formulation of meloxicam alone or in combination with tramadol in cats with naturally occurring osteoarthritis

Beatriz P Monteiro*, Mary P Klinck*,†, Maxim Moreau*,†, Martin Guillot*,†, Paulo VM Steagall‡, Daniel K Edge§, Jean-Pierre Pelletier†, Johanne Martel-Pelletier†, Dominique Gauvin*, Jérôme RE del Castillo* & Eric Troncy*,†

*Animal Pharmacology Research Group of Quebec (GREPAQ), Faculty of Veterinary Medicine, University of Montreal, Saint-Hyacinthe, QC, Canada

†Osteoarthritis Research Unit, Research Center of the University of Montreal Hospital Centre, Montreal, QC, Canada

‡Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Montreal, Saint-Hyacinthe, QC, Canada

§US Veterinary Operations, Zoetis, Inc., Florham Park, NJ, USA

Correspondence: Eric Troncy, Animal Pharmacology Research Group of Quebec (GREPAQ), Faculty of Veterinary Medicine, University of Montreal, PO Box 5000, Saint-Hyacinthe QC J2S 7C6, Canada. E-mail: eric.troncy@umontreal.ca

Abstract

Objective To evaluate the analgesic efficacy of meloxicam oral transmucosal spray (OTMS) alone and with tramadol in cats with osteoarthritis (OA).

Study design Randomized, blinded study.

Animals Fifteen geriatric cats weighing 4.5 ± 1.0 kg.

Methods Healthy cats with OA were randomly administered a placebo (every 12 hours orally) and meloxicam OTMS (approximately 0.05 mg kg^{-1} every 24 hours) (group M, $n = 7$), or tramadol (3 mg kg^{-1} every 12 hours orally) and meloxicam OTMS (group TM, $n = 8$) for 25 days. Evaluations performed before treatment (D0) and at week 3 (W3) consisted of peak vertical force, motor activity and response to mechanical temporal summation of pain (RMTS). Data were analyzed with mixed models and Fisher's exact test.

Results Mean ± standard deviation peak vertical force (percentage of body weight) increased significantly in both groups ($p = 0.02$), from 47.7 ± 6.5% to 60.5 ± 9.4% in group M, and from 51.8 ± 5.0% to 64.1 ± 6.5% in group TM, with no difference between groups. Motor activity increased in M (from 43 ± 12 to 56 ± 13; $p = 0.02$), but not in TM. The number of stimulations from RMTS increased in TM only. Cut-off values were reached in a larger number of cats ($n = 5$) in TM than M ($n = 1$) ($p < 0.05$). Gastrointestinal adverse effects were self-limiting in six cats, including five in TM.

Conclusions and clinical relevance Meloxicam OTMS had similar effects on peak vertical force, motor activity and pain sensitization as previously reported for oral meloxicam in OA cats. The tramadol–meloxicam combination provided no evident benefit over meloxicam alone, except for central hypersensitivity (assessed with RMTS). Further assessment of the potential toxicity of the combination is required prior to clinical use. Gingival administration was well accepted overall.

Keywords analgesia, degenerative joint disease, feline chronic pain, meloxicam, osteoarthritis, tramadol.

Introduction

Osteoarthritis (OA) is characterized by a pathological change in the joint. It is associated with pain, inflammation, peripheral and/or central sensitization and decreased mobility, which impact on activity and quality of life (Clarke & Bennett 2006; Gunew et al. 2008; Lascelles & Robertson 2010; Guillot et al. 2013, 2014). Radiographic evidence of OA has been observed in up to 61% of cats aged >6 years (Slingerland et al. 2011) and in up to 90% of cats aged >12 years (Hardie et al. 2002). Signs of OA are very subtle and unspecific in clinical practice. Client-based questionnaires and activity monitoring have been used to assess pain-induced behaviors in cats with OA (Lascelles et al. 2007; Slingerland et al. 2011). In the research setting, outcome assessment measures to characterize functional disability and maladaptive pain secondary to central sensitization have been validated (Guillot et al. 2012, 2013, 2014, 2015).

Traditionally, the treatment of OA-related symptoms such as pain and inflammation has been based on the use of non-steroidal anti-inflammatory drugs (NSAIDs) such as meloxicam (Lascelles et al. 2007; Gunew et al. 2008; Gowan et al. 2011; Benito et al. 2013; Guillot et al. 2013). Meloxicam is a COX-2 preferential NSAID with high oral bioavailability, efficacy, palatability and good tolerability (Lascelles et al. 2007; Gunew et al. 2008; Guillot et al. 2013). Meloxicam improves motor activity (Lascelles et al. 2007; Guillot et al. 2013), but does not change von Frey hypersensitivity assessments in cats (Guillot et al. 2013). A new oral transmucosal formulation of meloxicam has been approved by the US Food and Drug Administration (FDA) for the control of pain and inflammation associated with OA in dogs, but not in cats (Food and Drug Administration 2016).

Tramadol is a centrally acting analgesic that produces μ-opioid receptor activation and serotonin and noradrenergic reuptake inhibition (Raffa et al. 1992; Desmeules et al. 1996; Steagall et al. 2008). The analgesic effects of tramadol result from its active metabolites, such as O-desmethyl-tramadol (Desmeules et al. 1996). The drug has high bioavailability after oral administration and O-desmethyl-tramadol follows tramadol's disposition profile in cats (Pypendop & Ilkiw 2008; Pypendop et al. 2009). Use of the combination of tramadol and meloxicam has been recently reported in a case series (Steagall & Monteiro-Steagall 2013), but the efficacy of the combination in the treatment of feline maladaptive (chronic) pain is unknown.

The aim of this pilot study was to evaluate peak vertical force, motor activity and response to mechanical temporal summation of pain (RMTS) after administration of tramadol–meloxicam, and meloxicam alone. The oral transmucosal spray (OTMS) of meloxicam was used in this study. The study hypothesis was that in cats with naturally occurring OA, the co-administration of tramadol and meloxicam would provide similar or increased peak vertical force, motor activity and number of stimulations from RMTS in comparison with the administration of meloxicam alone.

Materials and methods

Animals and experimental protocol

The study was approved by the Institutional Animal Care and Use Committee (no. 1757) of the University of Montreal and animals were handled and housed according to the Canadian Council on Animal Care Guidelines.

According to the inclusion criteria, experimental cats were selected based on normal neurologic examination and normal clinical pathology evaluations [complete blood count, serum total thyroxine (T4), serum chemistry profile and urinalysis]. The cats were older than 10 years of age, with normal physical examinations except for clinical signs of OA (pain at joint palpation), and radiographic evidence of OA affecting at least one appendicular joint. Cats were sedated for radiology by intramuscular administration of medetomidine (0.02 mg kg^{-1}; Domitor 1 mg mL^{-1}; Zoetis Canada, Inc., QC, Canada) and morphine (0.2 mg kg^{-1}; Morphine Sulfate Injection, 10 mg mL^{-1}; Sandoz Canada, Inc., QC, Canada). Whole-body digital radiographs were analyzed by a board-certified radiologist (Guillot et al. 2012). Exclusion criteria were administration of an NSAID or a glucocorticoid within 4 weeks or 8 weeks, respectively, of the start of the study. Fifty-seven cats from a colony of geriatric research animals normally used for investigations related to cognitive function were screened. None of the cats had experimentally induced orthopedic disease. The cats were assessed as described. They were required to be friendly and to be interested in human interaction because they would be subject to constant handling during the study. Fifteen cats met the inclusion criteria and were included in the study.