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RESEARCH PAPER

Tramadol plus metamizole combined or not with anti-inflammatory drugs is clinically effective for moderate to severe chronic pain treatment in cancer patients

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Abstract

Objective To test the effectiveness and safety of tramadol plus metamizole combined or not with a non-steroidal anti-inflammatory drug (NSAID) for treating moderate to severe chronic neoplastic pain in dogs, and its impact on quality of life (QL).

Study design Prospective, uncontrolled, open-label, clinical study.

Animals Sixty nine client-owned dogs with multiple forms of cancer and visual analog scale (VAS) pain score ≥ 40 after receiving NSAIDs for at least 7 days.

Methods The MN group received metamizole + NSAID, MNT group received metamizole + NSAID + tramadol and MT group received metamizole + tramadol. Pain was scored by the 0 to 100 mm VAS (0 = no pain, 100 = worst pain) and analgesic therapy was considered effective if 25 mm differences in VAS scores were observed between day 0 and the follow ups. The QL was evaluated according to a 0 to 36 scoring method for dogs (0 = worst, 36 = best) and side effects were recorded. Data were registered at day 0 (baseline) and at the first and second follow ups (7 and 14 days after day 0, respectively).

Results The MN group had less analgesia at day 7 (25%) and day 14 (42%) than MNT (59%, $p = 0.0274$; 76%, $p = 0.0251$, respectively) and MT groups (69%, $p = 0.0151$; 81%, $p = 0.0341$, respectively). The QL scores were lower in the MN group at the first (score 23) and second follow up (score 26) than in MNT (27, $p = 0.0847$; 30, $p = 0.0002$) and MT (28, $p = 0.0384$; 31, $p = 0.0001$) groups. Side effects were more commonly observed in the MN group (87%) than in MNT (24%, $p < 0.0001$) and MT groups (25%, $p = 0.0003$) at the first follow up.

Conclusions and clinical relevance Tramadol plus metamizole combined or not with NSAID were well tolerated and clinically effective to treat moderate to severe pain in dogs with cancer and improved QL.

Keywords analgesia, canine, dipyrone, opioids, persistent pain, tumors.

Introduction

Cancer is the leading cause of morbidity and mortality in older companion animals (Lester & Gaynor 2000). Pain is observed in most of the patients in all stages of neoplastic disease (Withrow 2001; Gaynor 2008). Prolonged pain often worsens physical and functional conditions and compromises

quality of life (QL) since chronic pain results in psychomotor behavioral changes that are detrimental to the animal (Foley et al. 2006).

Symptoms of chronic pain are characterized by behavioral manifestations similar to depression that may be noticeable only for people familiar with the animal (Wiseman et al. 2001). Most of the pain scoring systems are based on human trials that evaluate pain intensity by self-report methods or were developed for dogs but are related to acute pain management (Mastrocinque & Fantoni 2003; Yazbek & Fantoni 2005a; Martins et al. 2010). In spite of outstanding advances in chronic pain diagnosis over the past years, as represented by structured questionnaires based on health-related QL in dogs (Wiseman-Orr et al. 2004, 2006; Yazbek & Fantoni 2005b; Hielm-Björkman et al. 2009), chronic pain still remains a significant problem in veterinary medicine (Wiseman et al. 2001).

In the treatment of neoplastic pain many animals are assisted in advanced stages of the disease, when cure is impossible and pain control and palliative care becomes the main goal during assistance (Gaynor 2008). Tramadol is a centrally acting analgesic that has weak opioid agonist properties and also has effects on norepinephrine and serotonin reuptake (Radbruch et al. 1996). This analgesic has an appropriate profile for long term analgesia considering it causes minimal cardiopulmonary depression and has no long term negative gastrointestinal, renal or coagulation effects (Williams 1997). In human patients with chronic neoplastic pain, tramadol produces effective analgesia with minimal adverse effects (Wilder-Smith et al. 1994). Tramadol may be combined with anti-inflammatory drugs for treating moderate to severe pain with dose reduction of opioids and a summation of effects due to their different mechanisms of action (Martins et al. 2010; Imagawa et al. 2011). Metamizole, a weak NSAID also known as dipyrone, has powerful pain relieving and antipyretic properties that seem to be related to the inhibition of COX-3 enzymes (Chandrasekharan et al. 2002). Previous studies showed appropriate post-operative analgesia with no laboratory parameters or clinical alterations provided by metamizole in dogs (Imagawa et al. 2011).

In dogs there are no specific studies evaluating the clinical impact of tramadol in dogs with chronic pain due to cancer although previous studies have proven its efficacy on postoperative pain relief in this species (Mastrocinque & Fantoni 2003; Yazbek & Fantoni 2005a; Martins et al. 2010). This study aimed to evaluate the efficacy and safety of tramadol in reducing moderate to severe chronic pain in dogs with cancer as well as its impact on their QL.

Materials and methods

Animals

The study was approved by the institutional animal care and use committee (protocol number 690/2005). All client-owned dogs that had a diagnosis of chronic oncologic pain were evaluated during the time of the study (from August 2005 to March 2007). Ten days after admission and pain therapy, the dogs were evaluated for enrollment in the study according to the inclusion and exclusion criteria established. Animals were only included in the study if they had: cancer confirmed by clinical examination and other evaluations such as radiography, ultrasonography, tomography, cytology or histopathology; moderate to severe pain (visual analog scale - VAS - pain score ≥ 40 according to the owner) unresponsive to treatment with metamizole (Novalgina, Bayer, Brazil) at a dose of 25 mg kg^{-1}, PO, every 8 hours or non-steroidal anti-inflammatory drugs (NSAID) carprofen (Carproflan, Agener União, Brazil) at a dose of 2.2 mg kg^{-1}, PO, every 12 hours or meloxicam (Maxicam, Ourofino, Brazil) at a dose of 0.1–0.2 mg kg^{-1}, PO, every 24 hours) for at least 10 days. Animals were excluded from the study if they were aggressive and did not allow appropriate evaluation, if they had a contraindication for NSAIDs (i.e. clinical signs of gastrointestinal, hepatic or renal disease), if they had been treated with opioids (including tramadol) in the last 10 days, if they were not properly medicated by the owner, if they had owners who were unable to return for weekly monitoring, if the owner had insufficient education to understand the pain score scale and QL questionnaire or if the owner was not familiar with the habits and behavior of the animal. Client consent was obtained before entry of any dog into the study.

Study design

"Admission" was considered as the first time that the dog was taken to the veterinary hospital at our institution. The 10th day after admission was considered as "day 0" (baseline); the first follow up, which occurred 7 days after day 0, was considered as "day 7"; the second follow up, which occurred 14 days after day 0 was considered as "day 14". At