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Original paper

Tramadol for the treatment of pain in companion animals

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Summary. For both medical and ethical reasons, the importance of providing effective pain relief for dogs and cats following surgical procedures or acute injury, as well as for those suffering from chronic medical conditions, is widely accepted. Tramadol is an opioid analgesic drug used in humans, which has become very popular in veterinary medicine. The aim of the present study was to analyze tramadol use patterns in small animal practice in Serbia in the context of current scientific literature. Study results show that the majority of prescriptions were written for dogs (65.8%) versus cats (34.2%). The most common treated conditions were digestive, orthopedic and neoplasia, etc. Regarding tramadol use, there is a large variation in administered dosage reported in the literature. Further studies are needed to fully describe the potential uses of tramadol in dogs and cats.

Keywords: cats, dogs, opioids, pain, prophylaxis, tramadol treatment.

INTRODUCTION

Pain alleviation is not only a professional obligation, but also significantly contributes to successful case outcomes and can adversely affect an animal's quality of life (Fox 2014; Epstein et al. 2015). Effective pain management involves a multimodal strategy using several classes of pain-modifying medications (Vedpathak et al. 2009; Epstein et al. 2015). The choice of medication used to treat pain should be based on the underlying cause of pain and anticipated pain levels as well as the individual patient's needs (Mathews et al. 2014; Epstein et al. 2015). Knowledge of the pharmacology of analgesic drugs in each species is required to optimize drug choice (Mathews et al. 2014). Interest in providing analgesia to veterinary patients has increased substantially over the past 20 years (KuKanich and Papich 2004; Flecknell 2008). For many years, animal pain management has benefited from the repurposing of analgesics previously approved for use in people (Flecknell 2008).

Opioids are the most effective drug class for managing acute pain and can play a role in managing chronic pain (Epstein et al. 2015). Tramadol is a centrally acting analgesic drug that has been in clinical use for the last two decades to treat pain in humans, and is starting to be widely used in veterinary medicine (KuKanich and Papich 2004; McMillan et al. 2008). Tramadol is used in veterinary medicine for the treatment of acute and chronic pain, including neuropathic pain (Matičić and Vnuk 2010). One advantage of tramadol for chronic pain treatment over many other opioids is the absence of strict regulatory measures with regard to its use (McMillan et al. 2008). In addition, this drug has become popular in veterinary medicine due to the relatively low in-

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cidence of gastrointestinal and cardiovascular side effects associated with long-term use (Smolec et al. 2018). Moreover, tramadol has a low abuse potential and is well-tolerated with a low incidence of adverse effects in humans vs. conventional opioids (KuKanich and Papich 2004; McMillan et al. 2008). Despite the lack of pharmacokinetic and pharmacodynamic data, tramadol has become increasingly popular for pain management in veterinary patients (McMillan et al. 2008).

Recent pharmacokinetic and pharmacodynamics studies in dogs suggest that tramadol may be safely and effectively used for various pain conditions in dogs (Lorimier and Fan 2005). As an analgesic, tramadol can be used alone to treat mild pain, although it does not provide adequate effects (Smolec et al. 2018). However, combination of tramadol with other analgesics, including NSAIDs, provides better analgesia (Lorimier and Fan 2005; Smolec et al. 2018). Because of its bitter taste, tramadol can induce profuse salivation and is often disliked by animals when they taste the drug (KuKanich 2013; MacFarlane et al. 2014). There are some data supporting tramadol use in clinical veterinary patients, but more studies need to be conducted to confirm its efficacy and safety in dogs and cats and to optimise its therapetic use (KuKanich 2013).

This drug is not registered for use in non-human species. In Serbia, tramadol is sold under the brand name Trodon®, and is available in oral and injectable form for human use (ALIMS 2016). Drugs approved for human use are frequently also used for "off-label" therapy of companion animals, such as dogs and cats (Hölsö et al. 2005). Off-label use is defined as the use of a drug outside of the scope of its approved label (EMA 2018). Administration of drugs previously approved for humans for the treatment of companion animals is regulated by law (MMDAS ©2005-2021). The first treatment option should be a veterinary drug approved for the particular animal species. If such a product is not available, another veterinary drug approved for another animal species should be used. In fact, based on the so-called cascade protocol, human drugs are allowed only if a suitable veterinary drug for another animal species does not exist (Hölsö et al. 2005; MMDAS ©2005-2021).

The aim of the present study was to estimate and analyze the consumption of human approved tramadol in companion animals and evaluate the use of tramadol in light of the current scientific literature.

MATERIALS AND METHODS

Data collection

The present study was conducted at a private veterinary ambulance in Novi Sad, Serbia. The subject of the study were companion animals (dogs and cats) treated with tramadol between January and March of 2020. Veterinarians usually keep an electronic database of medical charts for dogs and cats. Computerized information enables a computer search and transfer of information to various spreadsheets (e.g. Excel version 9.0). A computer search was performed to identify all animals treated with tramadol during the survey period. One hundred and five medical records that included dogs and cats were used. The following information regarding the use of tramadol was gathered: animal species, age, drug brand name, active substance, pharmaceutical form, dosage, duration of the treatment and treated condition, as well as route of administration.

Data analyses

Data were first analyzed and sorted at the species level (dogs vs. cats), followed by indication and whether it was administered by an oral or parenteral route. Each administration was then classified as either therapeutic or prophylactic by manual review of the medical charts: if tramadol was given to an animal for a condition, this was classified as a therapeutic treatment; while administration of animals with tramadol as a part of a surgical procedure (administrated prior, during or after the surgical procedure) was classified as prophylactic. The mean treatment period for each indication was calculated, as well as the dosage regime.

RESULTS

During the survey, 105 medical products containing tramadol were prescribed for dogs or cats between January and March of 2020. The majority of these prescriptions were written to dogs (65.8%), while 34.2% were for cats. Patient ages ranged from two months to 15 years. The dogs were classified into 10 breeds, whereas 29% (20/69) were crossbreeds (Fig. 1). The majority of cats were domestic, as shown in Fig. 2.

Table 1. lists the main indications for tramadol usage in the treatment of dogs, while the main treatment indications for cats are shown in Table 2. For dogs, tramadol was administered for therapeutic treatment in 56.5% of the cases (39/69), while for cat's therapeutic treatment represented 58.3% of the cases (21/36). In contrast, tramadol was administered for prophylactic (perioperative) purposes in 43.5% (30/69) of cases for dogs, versus 41.7% of cases for cats (15/36). Surgical procedures, which included interventions such as ovariohysterectomy, trauma, neoplasia and others, are shown in Table 3 and 4.

Regarding tramadol administration route, oral and parenteral routes of administration were distinguished. In dogs, the most common administration route was parenteral (63.8%), followed by oral (36.2%). However, in cats, only

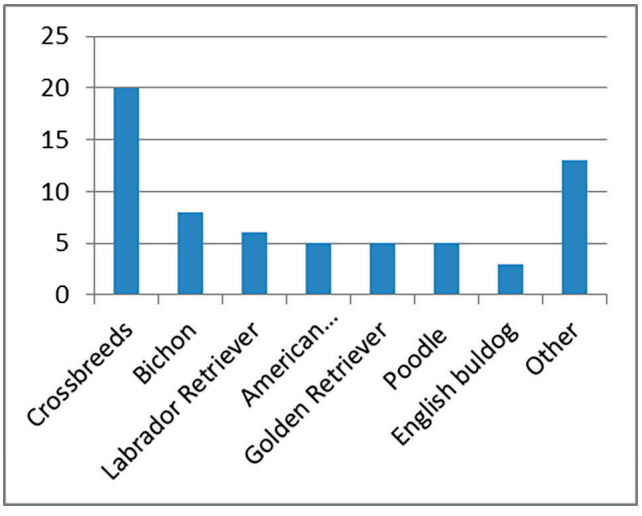

Fig. 1. Distribution of dog breeds.

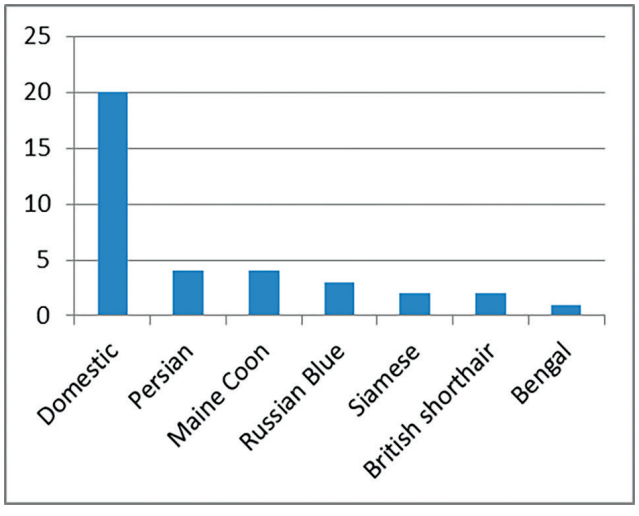

Fig. 2. Distribution of cat breeds.

Table 1. Distribution of tramadol administration to 69 dogs according to indication and route of administration.

Indication	Route of administration				N	%
	Peroral		Parenteral			
	N	%	N	%		
Osteoarthritis	3	42.9	4	57.1	7	10.1
Trauma	5	83.3	1	16.7	6	8.7
Pancreatits	3	60	2	40	5	7.2
Urolithiasis	–	–	3	100	3	4.3
Gastroenteritis	3	100	–	–	3	4.3
Discus hernia	2	100	–	–	2	3.0
Neoplasia	2	100	–	–	2	3.0
Cauda equina	1	100	–	–	1	1.4
Other	6	60	4	40	10	14.5
Surgery	–	–	30	100	30	43.5
Total	**25**		**44**		**69**	**100**

Table 2. Distribution of tramadol administration to 36 cats according to indication and route of administration.

Indication	Route of administration	%
	Parenteral	
Trauma	8	19.4
Gastroenteritis	4	13.9
Urolithiasis	3	8.3
Other	6	16.7
Surgery	15	41.7
Total	**36**	**100**

Table 3. Distribution of tramadol administration as prohylaxis for 30 dogs according to indication and route of administration.

Indication	Route of administration	%
	Parenteral (N)	
Ovariohysterectomy	9	30
Castration	7	23.4
Neoplasia	4	13.3
Laparatomia	3	10
Trauma	2	6.7
Fracture	2	6.7
Gastric torsion	1	3.3
Perineal hernia	1	3.3
Urinary obstruction	1	3.3
Total	**30**	**100**

Table 4. Distribution of metronidazole administered in surgery of 15 cats according to the indication in this study.

Indication	Route of administration	%
	Parenteral	
Ovariohisterectomy	7	46.7
Neoplasia	5	33.3
Urinary obstruction	2	13.3
Limb amputation	1	6.7
Total	**15**	**100**

parenteral tramadol was recorded. Dosage regime in dogs varied between 1-4 mg/kg/12 h, while 1-2 mg/kg/12 h was used in cats.

DISCUSSION

The treatment of pain in companion animals involves many of the same (or similar) drugs used for the treatment of pain in humans. Authorized medicines have been scientifically assessed according to statutory criteria for safety, quality and efficacy when used in accordance with the authorized recommendations on the product literature. Use of an unauthorized medicine provides none of these safeguards and may, therefore, pose potential risks that the authorization process seeks to minimize. Drugs approved for use in humans are frequently prescribed for companion animals all over the world, including Serbia. However, surveillance reports on the extent or nature of the usage of human approved drugs remains very limited. Tramadol is not approved for veterinary purposes, despite its common use in companion animal medicine. The percentage of tramadol prescriptions in the present study was significantly higher for dogs (65.8%), than cats (34.2%). Some conditions commonly treated with tramadol were ovariohysterectomy, osteorathritis and cancer related pain, in agreement with the findings of Evangelista et al. (2014) and Monteiro-Steagall (2016).

Opioids are widely used as a routine perioperative medicant to treat pain over the perioperative period (Evangelista et al. 2014; Epstein et al. 2015). According to the KuKanich and Papich (2004) tramadol has been effectively used for postoperative analgesia following orthopedic surgery and major gynecologic surgeries in addition to non-surgical conditions. Our study confirmed these findings. A study conducted by Ramsey (2010) has shown that tramadol 2 mg/kg provides equivalent analgesia to morphine 0.2 mg/kg i.v. after ovariohysterectomy. Tramadol has similar actions to morphine, but causes less respiratory depression, sedation and gastrointestinal side effects (Ramsey 2010).

With respect to administration route, in dogs the most common route of administration was parenteral (63.8%), followed by oral (36.2%), whereas cats were only treated with tramadol by parenteral injection (100%). This may reflect the challenge of giving oral medication to cats when compared to injectable agents (Burke et al. 2016), but also the fact that oral preparations are unpalatable to cats and therefore difficult to administer (Ramsey 2010; Macintire et al. 2012). Also, dosing with oral 50 mg formulations of Trodon® can be difficult (Ramsey 2010).

The recommended dose range is currently largely empirical due to a lack of pharmacokinetic and pharmacodynamic data for veterinary patients, and varies between 2-5 mg/kg/12 h for dogs and 1-4 mg/kg/12 h for cats (Matičić and Vnuk 2010; Ramsey 2011). Results from the present study revealed that veterinarians in Serbia follow similar dosage regime patterns for tramadol in dogs and cats.

CONCLUSIONS

Results from the present study indicate that tramadol is commonly used in small animal practice, although there are no reports available in Serbia about the extent and nature of tramadol use in small animal practice. Even though the sample size was small, no adverse effects of tramadol were reported during the study period, although studies in other Serbian cities are needed to confirm our findings. However, a centralized database is needed to enable estimation of the usage and therapeutic appropriateness of repurposing drugs approved for humans for use in the veterinary setting in Serbia.

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