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A BRIEF OVERVIEW OF THE COXIB DRUGS IN THE VETERINARY FIELD

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ABSTRACT

Traditional Non-steroidal Anti-Inflammatory Drugs (NAIDs) have been widely used to deal with many inflammatory conditions in veterinary medicine. Nowadays however, as the quality of life of animals is improved, new drug options need to be explored. In this review, the authors report on recent trends and the application of the active ingredients labeled for veterinary purposes.

Keywords: NSAID, Coxib, Veterinary Medicine

1. INTRODUCTION

In basic terms, inflammation is a protective reaction of the body against external and internal stimuli. In the acute phase, it serves to remove triggering agents in addition to restoring tissue following damage. However, if the inflammatory process becomes overwhelming, it results in pain through activation of nociceptors by various inflammatory mediators and eventually it can become life threatening and requiring of clinical intervention (Dubin and Patapoutian, 2010).

The Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) are used to treat pain, fever and inflammation in various diseases. Although the properties of NSAIDs may vary slightly between the diverse classes and generations, the main mechanism of action involves inhibition of Cyclo-Oxygenase (COX) in various organs. COX is the enzyme that converts Arachidonic Acid (AA) to form prostanoids, which are essential biological mediators including Prostaglandins (PG) and Thromboxanes (TX). In 1990, two decades after the discovery of COX, it was revealed that COX exists as two isoforms, COX-1 and COX-2 (Meek *et al*., 2010; Vonkeman and Laar, 2010). In brief, COX-1 is a constitutive enzyme found in many organs under normal conditions, while COX-2 is an enzyme up-regulated during inflammatory processes. Additionally in 2002, the third COX isoform (COX-3) was discovered. It is encoded by the same gene as COX-1, but COX-3, as a clinical target, is yet to be fully understood (Botting, 2003; Perrone *et al*., 2010).

In general, COX-1 is thought to be beneficial to the body's homeostasis with functions including maintenance of mucosal epithelium integrity, thus, its inhibition readily leads to gastric ulcers (Buvanendran, 2012). Inhibition of COX-2 only could decrease production of prostanoids such as PGE_2 and PGI_2 that are just involved in inflammatory and pathological processes, as well as ameliorate pain generation (Agarwal *et al*., 2009). Therefore, many clinical trials with NSAIDs focus on the selective inhibition of COX-2 enzymes because of the superior safety profile resulting from the COX-1 sparing effect.

Nowadays, there is a growing interest in animal welfare. Owners consider their pets as members of their families. The changed breeding environment and extended life span of pets has meant that they are predisposed to an extended spectrum of diseases for which owners are demanding a higher level of care. These trends have been an impetus for the development

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of more effective and innovative veterinary therapies (Giorgi, 2012; Giorgi *et al*., 2012a; Giorgi and Yun, 2012). However, veterinarians still have a reduced drug armamentarium compared to their human counterparts, thus, many studies have been conducted on the use of human medicine in the veterinary field (Giorgi *et al*., 2012b; Lavy *et al*., 2011). As use of selective COX-2 inhibitors (coxibs) became more prominent in human medicine, it followed that many selective inhibitors were introduced into clinical use for the veterinary market. Nowadays, many pharmaceutical companies have their own coxib drugs ("me too" drugs) and some of these active ingredients have been recently launched on the veterinary market.

However, animal species differences in factors such as the sensitivity and disposition of certain drugs could evoke unexpected results if they are used without any understanding of the drugs' behaviour in the target species (Martignoni *et al*., 2006; Giorgi *et al*., 2011; Toutain *et al*., 1997). In addition, to the best of the Authors' knowledge, the cardiovascular effects of coxibs during protracted therapy have not described in animals. In contrast, in the human field, coxibs have been reported to produce adverse effects on cardiovascular system such as thrombotic disorders including cerebral vascular events and myocardial infarction (Cairns, 2007; Batlouni, 2010). Furthermore, animals can be more sensitive to coxibs than humans due to differences in drug metabolism, absorption and enterohepatic recirculation (Bergh and Budsberg, 2005). For these reasons, knowing the pharmacological properties, pharmacokinetic/pharmacodynamic and safety profile of each drug is essential in order to use veterinary coxibs appropriately.

1.1. Classification of Coxibs

The coxibs are a subclass of NSAID which have a COX-1 sparing effects. Because of steric hindrance, the COX-1 active site is smaller than that of COX-2. The bulky structure of coxibs restricts their inhibition of COX-1 but allows for complete inhibition of the COX-2 pathway. The classification of NSAIDs is expressed as COX-2 selective, COX-2 specific, or COX-2 preferential. This indicates the drug selectivity for COX-2 and it is determined through calculation of the inhibitory concentration (IC_{50}) COX-1:COX-2 ratio (Bergh and Budsberg, 2005; Vane and Warner, 2000). However, these ratios have not been fully quantified and ratios for the same compound can be inconsistent, as the assays used were considerably different (Livingston, 2000; Pairet and Ryn, 1998).

Coxibs are regarded as a third generation of NSAIDs (Sternon, 2001). In the human field, several coxibs have been launched. The first to be launched were rofecoxib and celecoxib, these have been categorized as first generation. The newest active ingredients (valdecoxib, parecoxib, etoricoxib and lumiracoxib) have been classified as second generation and possess a stronger selectivity for the COX-2 enzyme inhibition (Stichtenoth, 2004; Andersohn *et al*., 2006). In veterinary medicine deracoxib (2002), firocoxib (2007), mavacoxib (2008) and robenacoxib (2009) have been introduced for animal use (Bergh and Budsberg, 2005). Recently, cimicoxib (2011) has also been introduced for the veterinary market from the human field (Emmerich, 2012).

1.2. Deracoxib

Deracoxib (Deramaxx®; Novartis) was the first coxib to be approved in veterinary medicine (Papich, 2008). Deracoxib contains a sulfonamide moiety. Chemically it is a 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazole-1-yl] benzenesulfonamide and its molecular weight is 397.38 g moL^{-1}. Deracoxib is categorized as a diarylheterocycle drug, these exert a time-dependent pseudo-irreversible inhibition of COX-2 (Walker *et al*., 2001). Deracoxib was initially approved for postoperative orthopedic pain in dogs at 3-4 mg kg^{-1} by oral (PO) daily dose for a maximum of 7 days. In 2003, deracoxib was also approved for chronic administration at a dosage of 1-2 mg kg^{-1} PO once daily (Smith, 2003).

In *in vitro* evaluations, among the coxibs, deracoxib was determined as a highly selective COX-2 inhibitor with a COX-1/COX-2 ratio of 1275 in purified enzymes assay (Gierse *et al*., 2002). However when tested using canine whole blood, the COX-1/COX-2 ratio was only 12 (McCann *et al*., 2004). This inconsistency resulted from the different types of cells with different cell conditions being used in each assay (Vane and Botting, 1995).

In another study using dogs, deracoxib showed the same degree of COX-1 and COX-2 inhibition as carprofen (COX-2 preferential drug), despite a wide variation of COX-1/COX-2 inhibitory ratios between the two drugs being found in *in vitro* assays (Sessions *et al*., 2005). These discordance results between *in vivo* and *in vitro* studies suggest that the *in vitro* results do not provide a quantitative measure of difference in efficacy or safety (Papich, 2008).

In the pharmacokinetic evaluation after oral administration of deracoxib (2~3 mg kg^{-1}) in dogs,

deracoxib had a protein binding affinity of over 90%. It also underwent hepatic biotransformation with an elimination half-life of 3 h, using biliary excretion as a major excretion route (Smith, 2003). After high-dose administration (8 mg kg^{-1}) however, a non-linear elimination has been shown: deracoxib loses its COX-2 selectivity and starts to inhibit COX-1 also (DCT, 2003). The nonlinearity at high doses might result from saturation of the metabolizing enzymes. In other species treated with deracoxib including cats (1 mg kg^{-1}) and horses (1~2 mg kg^{-1}), a longer half-life (7.9 and 12 h, respectively) than dogs was reported (Davis *et al*., 2011; Gassel *et al*., 2006). In cats and horses the hepatic enzymes, which participate in biotransformation of deracoxib, may be present at lower concentrations than in dogs and might therefore be saturated at lower concentrations, which leads to the longer half-life (Davis *et al*., 2011).

Clinical trials in dogs showed that deracoxib (1~2 mg kg^{-1} PO for 3 days) was able to reduce postoperative pain and inflammation after dental extraction surgery (Bienhoff *et al*., 2012). In addition, Millis *et al*. (2002) reported that the administration of deracoxib (1, 3, or 10 mg kg^{-1} PO) was more effective in reducing pain associated with urate crystal-induced synovitis than carprofen (2.2 mg kg^{-1} PO). Deracoxib treatment also showed no significant adverse effects (Millis *et al*., 2002).

After 28 days of once daily administration of deracoxib (1.6 mg kg^{-1} PO), it was shown to be safer than aspirin in regards to risk of gastric ulceration in healthy dogs (Sennello and Leib, 2006). In addition, long-term therapy of deracoxib for up to 6 months administered at the labeled dose, was found to be safe and well tolerated in dogs without any significant nephrotoxicity (Roberts *et al*., 2009). On the contrary, at higher than labeled doses or when given with other NSAIDs or corticosteroids, deracoxib has been found to cause gastrointestinal perforations in dogs (Lascelles *et al*., 2005).

Even though there has been no significant instances of hypersensitivity reported thus far, the administration of sulfonamide coxibs in animals allergic to sulfonamides should be carefully considered. Indeed it might be likely a cross reaction with other sulfonamides such as antimicrobial or an evocation of hypersensitivity (Shapiro *et al*., 2003; Sanchez-Borges *et al*., 2004; Bergh and Budsberg, 2005; Ayuso *et al*., 2013). The hypersensitivity of sulfonamide coxib such as deracoxib is yet to be confirmed.

1.3. Firocoxib

Firocoxib (Previcox®; Meriel) was developed specially for the veterinary field (for dogs and horses). It was found to be 350~430 fold more selective for COX-2 than COX-1 in *in vitro* canine whole blood assays (McCann *et al*., 2004). Chemically it is a 3-cyclopropymethoxy-5,5-dimethyl-4-[4-(methyl sulfonyl) phenyl]-2-(5H)-furanone and its molecular weight is 336.402 g moL^{-1}. The drug was launched several years ago and in this short time, the pharmacokinetic properties of firocoxib in dogs and horses have already been well established (Kvaternick *et al*., 2007a; 2007b; Letendre *et al*., 2008). Firocoxib is available as a chewable tablet oral preparation which has been approved in the European Union for dogs at a once daily administration of 5 mg kg^{-1}. In addition, firocoxib, as an oral paste was approved by FDA for the control of pain and inflammation associated with osteoarthritis in horses at 0.1 mg kg^{-1} once daily (Kvaternick *et al*., 2007b). In dogs, following PO administration (5 mg kg^{-1}), firocoxib was well absorbed and eliminated by hepatic metabolism and fecal excretion with an elimination half-life of 8 h (Kvaternick *et al*., 2007a). Firocoxib in horses (0.1 mg kg^{-1}) showed a bioavailability of 79% and an elimination half-life of 30 and 34 h for oral and intravenous administration, respectively. Due to its lipophilic and non-ionizable nature, firocoxib was widely distributed with a volume of distribution value of 1.7 L kg^{-1} after intravenous administration in horse. Firocoxib showed a longer half-life compared with other NSAIDs, such as phenylbutazone and flunixin meglumine (Kahn and Line, 2010; Kvaternick *et al*., 2007b).

A clinical study including 1,000 dogs treated for a 40-day period, reported that withdrawal rate due to development of gastrointestinal side effects was only 2.9%. Over 90% of investigators and owners rated improved clinical scores after firocoxib treatment (Ryan *et al*., 2006). In a long-term study over 52 weeks of treatment, a slight increase in withdrawal rate (5.1%) was reported due to GI signs (Autefage *et al*., 2011). Steagall *et al*. (2007) evaluated the adverse effects of oral firocoxib in healthy dogs for 29 days and found that a dose of 5.3±0.34 mg kg^{-1} of firocoxib did not cause any adverse effects on the GI tract or serum biochemical variables and was well tolerated in terms of hematological signs including platelet aggregation and buccal mucosal bleeding time index (Steagall *et al*., 2007). Firocoxib was found to be effective in a 90 day

long-term study performed on relatively geriatric dogs (over 7 years) affected by osteoarthritis. The side effects reported (minimal biochemical changes and diarrhea) were thought to be due to age-related deterioration in liver and renal functions (Joubert, 2009). Furthermore, in the sodium urate crystal-induced synovitis model, firocoxib treatment (5.3~6.49 mg kg^{-1}) resulted in reduced lameness and increased weight-bearing at both 3 and 7 h post-treatment, as compared with carprofen. Firocoxib efficacy was similar to dogs treated with vedaprofen but without any cardiovascular effects (Hazewinkel *et al*., 2008).

However, in developmental toxicity studies firocoxib showed embryotoxic and foetotoxic effects in both rats and rabbits, inducing a variety of malformations and anomalies. Consequently firocoxib, as with other coxibs, is contraindicated for use during pregnancy and lactation in dogs. Furthermore, firocoxib had a low safety margin in puppies compared to older dogs. Thus, like other drugs, its use in very young animals requires careful monitoring EMEA, 2006.

1.4. Mavacoxib

Mavacoxib (Trocoxil®; Pfizer) is a long acting coxib which has a chemical structure of 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide, it has a molecular weight of 385 g moL^{-1} and it acts as a preferential rather than selective COX-2 inhibitor if compared with carprofen. It is approved for the treatment of canine osteoarthritis requiring long-term treatment between 1 and 7 months EMEA, 2008. Mavacoxib is produced in a diverse range of tablets (6, 20, 30, 75 and 90 mg) as an oral chewable form. Unlike other coxibs, mavacoxib is recommended for monthly administration at 2 mg kg^{-1} because of its long half-life. In order to achieve steady-state concentrations, it is recommended that mavacoxib is administered with a 2-week interval between the first and second dose with monthly dosing thereafter.

The pharmacokinetics profile of mavacoxib has been well described in Beagle dogs (Cox *et al*., 2010). It showed significant low clearance rate (2.7 mL/h/kg) with a large volume of distribution (1.6 L/kg) in experimental intravenous administration. Especially in terminal half-life, all PO treated Beagle dogs (n = 63) showed an average value of 16.6 days with individual values ranging from 7.9 to 38.8 days. The half-life differences between individuals should be considered as a significant factor in the use of this drug. In fact, in individuals demonstrating a poor elimination rate this drug could evoke cumulative side effects. Moreover, it has been reported that food intake significantly affects mavacoxib absorption. The administration of mavacoxib (4 mg kg^{-1}) in fasted and fed dogs resulted in a bioavailability of 46.1 and 87.4% respectively. In field trials, mavacoxib showed a terminal elimination plasma half-life of 44 days in the target population, however 5% of dogs had an extended half-life of 80 days. In addition, most animals treated with 2 mg kg^{-1}, maintained trough plasma mavacoxib concentrations associated with efficacy (Cox *et al*., 2011).

As the safety profile has not been established in reproductive toxicity, application of mavacoxib to pregnant or breeding animals should be avoided. Furthermore, this kind of drug, which has a long half-life, should be carefully handled because of the potential for prolonged exposure.

1.5. Robenacoxib

Robenacoxib (Onsior®; Norvatis) is a coxib which has been developed solely for use in veterinary medicine and is the only approved coxib in cats available as a tablet as well as injectable form (King *et al*., 2009). It is recommended at a dose of 1~2 mg kg^{-1} once daily for both species. It has a chemical structure of 5-ethyl-2-[(2, 3, 5, 6-tetrafluorophenyl)amino]-phenyl acetic acid and a molecular weight of 327.27. Robenacoxib is a weak acidic drug (pKa 4.7) which has high protein-binding affinity (>98% in dogs) (Jung *et al*., 2009). In the *in vitro* COX-2 selectivity comparative study in dogs with whole blood assay, the IC_{50} ratio (COX-1:COX-2) was highest in robenacoxib (128.8) when compared to other NSAID such as deracoxib (48.5), nimesulide (29.2) and meloxicam (7.3) (King *et al*., 2010). In cats, robenacoxib also showed more COX-2 selectiveness (32.2) compared with diclofenac (3.9) and meloxicam (2.7) (Schmid *et al*., 2010a).

Previous studies have revealed its pharmacokinetic properties via different administration routes including, intravenous, subcutaneous and oral administration in the dog and cat (Jung *et al*., 2009; Pelligand *et al*., 2012). In dogs, robenacoxib showed good bioavailability after oral (84%) and subcutaneous (88%) administration with a short blood half-life of 1 h (Jung *et al*., 2009). In addition, Silber *et al*. (2010) revealed that robenacoxib remained longer in inflamed synovial joints than blood. The anatomically focused persistence of robenacoxib may be triggered by its weak acidity and high protein-binding affinity. In an inflamed area, the blood supply is increased and pH has become mildly acidic. These

alterations allow robenacoxib to enter cells more readily than under normal conditions. The ion-trapping due to the pH change slows release of the drug and as a result, intracellular drug concentrations increase (Brune and Furst, 2007).

In a clinical study, Schmid *et al*. (2010b) reported that SC injection of robenacoxib exerted analgesic and anti-inflammatory effects in the urate synovitis model at dosages of 0.25-4 mg kg^{-1} without COX-1 inhibition (Schmid *et al*., 2010b). In comparison with carprofen, robenacoxib also demonstrated good efficacy in field trials when given once daily (Reymond *et al*., 2012). Furthermore, robenacoxib provided similar efficacy and tolerability to meloxicam in controlling perioperative pain and inflammation in dogs (Gruet *et al*., 2011). In cats after ovariohysterectomy surgery, SC injected robenacoxib (2 mg kg^{-1}) provided a greater analgesic effect for up to 24 h compared to buprenorphine (Staffieri *et al*., 2013). According to the study from King *et al*. (2012), as expected, robenacoxib had an excellent safety profile in young healthy cats when administered at daily dosages up to 10 mg kg^{-1} for 28 days and up to 20 mg kg^{-1} for 42 days (King *et al*., 2012). Also in dogs, robenacoxib showed high safety index without any relevant toxicity with daily dosages as high as 40 mg kg^{-1} for one month and 10 mg kg^{-1} for 6 months (King *et al*., 2011). This proven safety of robenacoxib may result from its high COX-2 selectivity and rapid central compartment clearance with longer residence at inflamed sites (King *et al*., 2012). However there is no data on reproductive toxicity and robenacoxib should not be used in pregnant or breeding animals.

1.6. Cimicoxib

Cimicoxib (Cimalgex®; Vetoquinol) is a novel imidazole derivative coxib and a highly selective COX-2 inhibitor, that has recently been launched (Emmerich, 2012). Chemically it is a 4-[4-Chloro-5-(3-fluoro-4-methoxyphenyl)-1H-imidazol-1-yl]benzenesulfonamide and its molecular weight is 381.809 g moL^{-1}. Although it was originally developed to treat depression and schizophrenia, this compound showed good oral activity when tested in experimental models of acute and chronic inflammation and pain (Haroon *et al*., 2012). After some years of human clinical studies on its anti-inflammatory and analgesic properties, cimicoxib was redirected from the human to the veterinary field.

Cimicoxib is available as chewable oral tablets licensed for dogs as a once daily administration given at a dose of 2 mg kg^{-1}. Due to its recent release, there is very little published data available. Recently an analytical method for cimicoxib pharmacokinetic study has been published (Giorgi *et al*., 2013). Sorbera and Ramis (2004) found that cimicoxib was more metabolically stable than celecoxib. In humans, cimicoxib undergoes demethylation and a subsequent conjugation reaction, the demethylated metabolite of cimicoxib has been found to be inactive in both COX-1 and COX-2 activity assays. In rats after oral and i.v. administrations, biliary excretion was the major route of elimination. 70 and 30% of the Cimicoxib dose was excreted in the feces and urine respectively. In Beagle dogs, the bioavailability was 75% following oral administration (1 mg kg^{-1}) with t_{max} of 2 h and $t_{1/2}$ of 7 h. Like in rats, biliary/intestinal excretion was the major route of elimination in Beagle dogs and cimicoxib was extensively metabolized, as <0.2% unchanged drug was detected (Sorbera and Ramis, 2004). In an *in vivo* inflammatory acute pain model study, 10 h after administration (2 mg kg^{-1}) the plasma concentrations were above a level of 100 ng Ml^{-1} (the EC_{50}/IC_{50} values varied between 216 and 452 ng mL^{-1} for different parameters) in six out of ten animals. At 24 h, the concentrations are lower than the stated EC_{50}/IC_{50} values in all animals. Considering the estimated differences in bioavailability and correcting for non-linear PK, it appeared that the effect of cimicoxib lasted for approximately 10-14 h in the simulated inflammatory acute pain model EMEA, 2009. In addition, the non-inferiority study where it was compared with firocoxib confirmed that cimicoxib reduced the clinical signs of disease including lameness, pain, locomotor disturbance and oedema in dogs with chronic osteoarthritis during the 90 days of the follow up study. Furthermore, compared with carprofen, cimicoxib was also effective in peri-operative pain control in orthopaedic or soft tissue surgery during the first 24 h after surgery EMEA, 2009.

In a 26 week tolerance study with Beagle dogs, it was demonstrated that adverse effects occur on the gastrointestinal tract and to a lesser extent the kidney especially papillary necrosis at higher doses (10 mg kg^{-1}). However, there were no significant adverse signs in the recommended dose group (2 mg kg^{-1}) and notably, there were no cardiovascular events. The reproductive toxicity study with rabbits however, revealed that the cimicoxib affects fertility and fetal development. Since there are no data in pregnant bitches, “caution” or “cimicoxib is contraindicated in” is needed in breeding, pregnant and lactating dogs EMEA, 2009.

2. CONCLUSION

It is complicated work to make firm distinctions between preferential and selective COX inhibition or between nonselective and preferential inhibition. This is because 1. Potency ratios (COX-1:COX-2) vary widely according to experimental conditions both within and between laboratories, 2. the ratio calculated may vary depending on whether it is based on 50, 80, 95 or some other percentage inhibition and 3. apparent species differences in inhibition ratios (Lees *et al*., 2004; Giraudel *et al*., 2009). However, classification of coxibs is mostly academic and for the purposes of drug categorization. The most important thing is to understand the pharmaco-physiological properties of each coxib in order to make the appropriate choice for each situation. In addition, to secure the expanded list of drugs for veterinary use, trials for adaptation should be on going.

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