

Veterinary Medical Teaching Hospital
University of California, Davis

Animal Pharm News

A newsletter from the pharmacy department

Evolution of NSAID use in Canine Osteoarthritis

By Valerie Wiebe, PharmD

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Osteoarthritis (OA) is a slowly progressive, degenerative joint disease estimated to affect 20% of adult dogs. The disease is associated with an imbalance between the amounts of proteolytic enzymes and their inhibitors, mediated by proinflammatory cytokines. Risk factors involve increased age, excessive weight and breed susceptibility. Current treatment strategies are limited to surgery or management of chronic pain using nonsteroidal anti-inflammatory drugs (NSAIDs) or nutraceutical products. Although surgery is extremely beneficial in some animals, not all are candidates for surgery. While nutraceuticals frequently have limited efficacy and high variability between products (see below), therapy often involves the use of NSAIDs.

The use of NSAIDs in canine patients was contraindicated prior to 1997 due to the extreme sensitivity of this species to the gastrointestinal (GI) side effects of these agents. Non-selective NSAIDs (ibuprofen, naproxen) labeled for use in human osteoarthritis were associated with ulcer production and even GI perforation in dogs. In 1997, Pfizer pharmaceuticals was the first to market a veterinary (continued on page 3)



What to Know Before Recommending Nutraceuticals

By Margo Karriker, PharmD

The North American Veterinary Nutraceutical Council defines a nutraceutical as a “non-drug substance that is produced in a purified or extracted form and administered orally to provide agents required for normal body structure and function with the intent of improving the health and well-being of animals.” Due to a continued emphasis on health and nutritional supplements, pet owners see that an important role in pet ownership is to provide their companion with optimal nutrition and nutritional supplements. As a result, veterinarians and pharmacists will be required to make decisions and evaluate the safety of available nutraceuticals for animals.

The Dietary Supplement Health and Education Act (DSHEA) was passed by congress in 1994. The goal of this act was to facilitate the availability of nutritional products for humans; however, the FDA-Center for Veterinary Medicine interprets this act as inapplicable to animal products. Scientific information and clinical trial data is not often available for nutraceuticals and commonly there is a significant lack of information on the basic properties and functions of these substances. This

leaves the veterinary practitioner with many unanswered questions when faced with recommending natural products. Here are a few tips and examples of how to evaluate a natural product and its place in therapy.

- **Efficacy-** The most important point to consider when evaluating a product is efficacy. There is a continuing effort on the part of manufacturers to validate the use of their product and prove efficacy. This practice has provided a growing body of literature on the use of nutraceuticals in clinical situations. Unlike FDA-approved medications, there is no legislation or regulatory agency that requires these products to provide efficacy data prior to marketing these products. Generating efficacy data is often a rigorous, cost-prohibitive, time-consuming process and a lack of available data is the result. Veterinarians should always consult the product manufacturer when questions arise. A reputable company should be able to provide efficacy information. Clinicians should remember to check the product’s active ingredients and ask questions. Does this product contain one

Recommending a Nutraceutical (continued from page 1)

active component or several? Is the proposed mechanism of the product likely to treat the desired symptoms? Has this product been studied in the species of interest? Were the studies conducted under standard conditions? Was this study biased in any way including sponsorship from the manufacturer?

- **Product quality** – Since no government authority oversees the manufacture of these products, it is up to the clinician and consumer to discern the quality of the product. Each product should be manufactured under strict procedures. A company that will not provide evidence of good manufacturing processes should be avoided. The manufacturer should have knowledge of the product's purity and content of active product. A recent study analyzed the content of 11 over-the-counter products that contained chondroitin, glucosamine or both for use in horses. Based on the amount of ingredient listed on the label, the amounts of actual ingredient ranged from 63.6% to 112% for glucosamine and 22.5% to 155.7% for chondroitin. The price of the product did not correlate to the % of listed ingredient. Product distributors

and manufacturers should be eager to share all information concerning the quality of their products.

- **Safety**– Safety, when used in a true clinical situation, should be considered. Often, historical or anecdotal information on short-term dosing provides the clinician with a false sense of safety when considering long-term therapy. Few clinical studies follow veterinary patients during long-term nutraceutical use. There is ample evidence documenting significant drug interactions with various natural products. Accidental ingestion of large quantities of these products or megadoses have the potential to have toxic effects. Before suggesting supplements, clinicians should investigate any concomitant medication interactions. The most important rule of safety of nutraceuticals is to consider all supplements, including food supplements, in the same way a traditional drug product would be investigated.

Veterinarians have an ever increasing responsibility to gain knowledge about natural products and nutraceuticals. As marketing efforts to promote these products become more prevalent, clinicians will need to become increasingly more familiar with how natural products and nutraceuticals can complement traditional therapies.

Prevention and Treatment of NSAID induced Peptic Ulcers

By: Valerie Wiebe, Pharm.D.

Nonsteroidal anti-inflammatory drug (NSAID) induced peptic ulcers are the result of prostaglandin (PG) inhibition. PG production is necessary for gastric mucosal defense in the stomach where it enhances mucosal blood flow and stimulates mucus production and bicarbonate secretion. PG inhibition in the gastrointestinal (GI) tract results in the weakening of mucoid defenses and potentiation of gastric and duodenal ulcers.



Prevention

The initial approach toward prevention of NSAID-induced ulcers should be directed toward identification of animals that may be at greatest risk for NSAID-induced ulcers (older dogs, prior GI disease, cancer, concurrent use of gastrointestinal irritating drugs, etc.). In these patients prophylaxis should be strongly encouraged. For prevention of NSAID induced ulcers both proton pump inhibitors (PPI's)

and misoprostol are useful. In human studies, the PPI (omeprazole) was better tolerated and associated with a lower relapse rate than misoprostol (1).

Although, no data are available demonstrating an advantage of PPI's over misoprostol in NSAID induced ulcers of canine, the improved availability of omeprazole (Prilosec) (now sold over the counter), reduced cost, better compliance, and limited side effect profile of PPI's provides significant advantages to PPI's in this setting.

Treatment

Mild NSAID induced ulceration that is uncomplicated may heal after discontinuation of the NSAID and treatment with histamine-2 (H-2) blockers, proton pump inhibitors or sulcrafate. In humans, sulcrafate and H-2 blockers have demonstrated efficacy in reducing the symptoms of dyspepsia and gastrointestinal irritation but have little efficacy in helping to heal NSAID induced ulcers compared to the proton pump inhibitors (PPI). For treatment of large, refractory or complicated ulcers, twice daily treatment using a PPI is generally considered the treatment of choice in humans.

References

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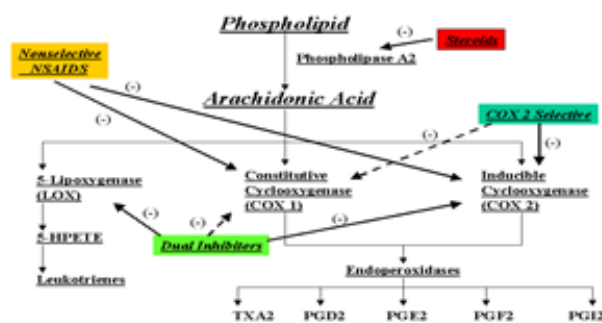
Tips and Reminders

By: Pharmacy staff

Here are a few friendly tips and reminders to help us best accommodate your pharmacy needs:

- **Dispensing Fees:** A dispensing fee is applied to each medication ordered. For example, an order for two different medications would have a dispensing fee included in the cost of each medication. It is most economical to estimate, as closely as possible, the amount of medication needed.
- **Controlled drug orders:** Please remember that Schedule II controlled drug orders must be written on a separate order slip from other medications. These require separate filing according to the Board of Pharmacy and therefore, must be written as a separate order. This does not apply to chart orders for drugs to be dispensed from the Omnicell machines.
- **Writing prescriptions for outside the VMTH:** A prescription that is to be filled outside of the VMTH must be written by a DVM licensed in the state of California.
- **Doses written as SID:** A prescription written for SID dosing will not be recognized as “once daily” by most pharmacists. In human medicine, there is no SID abbreviation. Additionally, SID will often be interpreted as QID, which is four times daily, resulting in a 4-fold increase in dose. Please be especially conscious of this as you write prescriptions to be dispensed outside of the VMTH. It is best to get into the practice of writing out “once daily”, “once per day”, “q 24 hours”, or “every 24 hours”.
- **Legible handwriting:** Many errors can occur due to poor handwriting. As more medications come to the market with similar names and similar doses, it becomes harder to translate poorly written orders. Abbreviations are also a frequent source of error. Please write out abbreviations such as: “Once daily” instead of SID, “two grams” in place of “2g”. Ideally, no numbers or abbreviations would be used when writing prescriptions; however, clear, neat handwriting can substitute, if necessary. Remember to write legibly!

Figure 1: Pharmacological actions of selective NSAIDs



NSAID Evaluation (continued from page one)

labeled NSAID that could be used safely in dogs. Their product, carprofen (Rimadyl) was noted to effectively inhibit prostaglandin (PG) synthesis at sites of inflammation but “spare” inhibition of protective PG’s in the GI tract.

Further study of the arachidonic acid pathway began to shed even more light on the exact enzymes involved in the inflammatory cascade, and which enzymes were the ideal target for NSAIDs. It was found that there was not one, but two isoforms of the cyclooxygenase (COX) enzyme that had traditionally been the target of NSAIDs. The COX 1 isoform was noted to be the constitutive enzyme, predominantly expressed in the GI tract. Inhibition of COX 1 was noted to be associated with NSAID induced GI prostaglandin inhibition and ulcer production. Conversely, the COX 2 isoform was found to be inducible locally during inflammation, making it an ideal target for achieving anti-inflammatory effects.

With this new information, pharmaceutical companies began to target the COX 2 isoform and look for products that selectively inhibited COX 2. Novartis Animal Health then came out with deracoxib (Deramaxx) the first veterinary labeled NSAID to specifically target the canine COX 2 enzyme. Deramaxx, which was originally labeled for control of post operative inflammation and was then approved for chronic use in inflammation associated with canine osteoarthritis.

Serendipitously, two other products, Etodolac (Fort Dodge) and Meloxicam (Boehringer Ingelheim) were then found to be COX 2 selective. Controversy has surrounded the COX 2 specificity of meloxicam which loses its COX 2 specificity at higher doses (1). Both meloxicam and etodolac have been used in humans and both have shown less gastric damage than non-selective NSAIDs, but residual GI toxicity remains problematic (continued page 4).

More on NSAIDs (continued from page 3)

Dual Inhibitors

A subsequent pathway involving metabolism of arachidonic acid by the enzyme lipoxygenase (LOX) into leukotrienes was also demonstrated to occur at sites of inflammation. Inhibition of leukotriene synthesis is now reported to be more effective at reducing inflammation than COX inhibition in human rheumatoid arthritis patients. Although specific lipoxygenase (LOX) inhibitors are not yet available on the veterinary market, a “dual” inhibitor, Zubrin (Schering-Plough Animal Health) that selectively inhibits both COX-2 and LOX enzymes has recently been approved. The simultaneous inhibition of 5-lipoxygenase is believed to prevent the pro-inflammatory and gastrointestinal damaging effects of leukotrienes (2).

NSAID induced Gastropathy

While the overall incidence of gastropathy has significantly declined with the use of COX 2 selective NSAIDs it still remains the primary side effect. Severe toxicity, including GI ulceration and perforation may still occur but are rare and primarily noted in patients with concurrent disease (renal and hepatic failure, inflammatory bowel disease, cancer). Other risk factors include increased age, history of GI ulcers, and concurrent steroids, aspirin or other NSAIDs. In these patients it is advised to prophylax with a GI protectant such as a proton pump inhibitor or misoprostol (See page 2).

Interesting new data now suggest that COX 1 selective inhibitors do not cause GI injury alone and ulcer promotion may actually require both COX I and COX 2 inhibition. In the presence of gastric injury, COX 2 induction produces anti-inflammatory PG's (PGD2 and PGF2) which promote healing (3). Following gastric injury, COX 2 inhibitors have been shown to retard ulcer healing and reactivate ulcers at the site of a previous scar (4). This may explain some of the difficulties in assessing COX 2:COX 1 ratios as a predictor of gastrointestinal toxicities, aside from their dose dependent COX-2 specificity.

Renal Toxicity

While all NSAIDs have the potential to induce renal dysfunction via PG inhibition, COX-2 selective NSAIDs may have a greater overall risk. In times of physiologic stress, the COX 2 isoform is predominantly expressed in the canine kidney during autoregulation of renal blood flow (5). In the setting of dehydration, hemorrhage, hemodynamic compromise, heart failure, liver disease, and renal disease, circulating vasoconstrictors act to retain vascular resistance at the expense of blood flow to the kidneys. Administration of COX 2 selective NSAID's under these circumstances may compromise blood flow to the kidney and result in acute ischemic renal failure and papillary necrosis. Renal toxicity is reversible in most cases, with discontinuation of NSAIDs

and hydration, but has been fatal in some animals. Baseline renal panels and close monitoring of serum creatinine and BUN are recommended.

Hepatocellular Toxicity

NSAID induced liver disease is extremely rare in dogs (carprofen incidence=0.02%), but may be fatal. In humans, NSAID induced hepatic reactions are considered a class characteristic of all NSAIDs. The incidence of toxicosis from individual drugs has been directly correlated with frequency of use and monitoring of ALT and bilirubin. Elevations of serum ALT and AST may occur in up to 15% of patients receiving NSAIDs, but < 1% actually demonstrate the greater than 3 fold elevation from baseline levels indicative of liver disease. In general, the relative risk is low but may increase with concurrent hepatotoxic drugs. The exact mechanism of hepatotoxicity is unknown but may involve idiosyncratic (immune/metabolic), and/or intrinsic (dose-related) mechanisms.

In a retrospective review of 21 dogs (ages 4-15) with suspected carprofen induced liver toxicosis, clinical signs were noted in 18/21 dogs 5-30 days (mean 19.7 days) after starting treatment. Predominant signs were: anorexia (17), vomiting (16), lethargy (8), and diarrhea (8). The majority of dogs (17/21) recovered on supportive care (fluids/antibiotics/nutritional support). Baseline liver function tests and monitoring may help to identify patients before fulminate liver toxicity occurs.

Generic Name	Brand Name	Oral Formulation	Dose (daily)	Cost (40kg x 30 days) (VMTH)
Carprofen	Rimadyl	Chewable tablets	4.4 mg/kg	\$55.00
Deracoxib	Deramaxx	Chewable tablets	1-2 mg/kg	\$33.00- \$61.00
Etodalac	Etogesic	Tablets	10 mg/kg	\$46.00
Meloxicam	Metacam	Suspension	0.1 mg/kg	\$97.00
Tepoxalin	Zubrin	Disintegrating tablets	10 mg/kg	\$73.15

Table 1: Product Comparison Chart

References

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2. Bertolini A, et al., Pharmacol Res 2001; 44(6): 437
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