SWITCHING
NSAIDS IN DOGS

A guide brought to you by Vetoquinol UK and Duncan Lascelles, BSc, BVSc, PhD, FRCVS, CertVA, DSAS(ST), DECVS, DACVS Professor of Translational Pain Research and Management.

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INTRODUCTION

Non-steroidal anti-inflammatories (NSAIDs) are an important therapeutic tool in treating pain associated with osteoarthritis (OA) in dogs. There is strong scientific evidence that they provide beneficial analgesic effects in dogs with OA-pain[1;2]. On a group basis, the benefit of NSAIDs is clear, but individual animal response – both for efficacy and adverse events – varies. Individual dogs may not respond to a particular NSAID; side effects related to the administration of a particular NSAID can occur; and, although poorly documented, in some animals, analgesic efficacy appears to wane over time. These factors lead clinicians to consider switching dogs from one NSAID to another.

During the process of switching, a temporal gap, or 'washout', between different drugs is often considered. The 'washout time' is the period between administrations of an NSAID when switching from one drug to another. Information published by veterinary pharmaceutical companies has advocated such a washout period and VMD approved wording in product SPCs consistently state that "pre-treatment with other anti-inflammatory substances may result in additional or increased adverse effects and accordingly a treatment-free period with such medicinal products should be observed before the commencement of treatment with another NSAID".

This narrative will discuss recommendations around switching between NSAIDs, including the washout period. There is little scientific evidence on this topic, and so where statements are not referenced, readers should consider the text to be based on personal opinion.

REASONS FOR CONSIDERING **SWITCHING BETWEEN NSAIDS**

SIDE EFFECTS

As reviewed and discussed in detail in a recent paper[3], adverse effects can occur with NSAIDs, but the overall incidence is probably very low. Indeed, in the randomized, placebo-controlled, blinded studies (n = 25) that were reviewed, the incidence of adverse effects was not statistically different between treated and control dogs. However, no studies have been appropriately powered to determine the true incidence of adverse events with NSAIDs compared to placebo[3]. Overall, most consider that the NSAIDs approved for use in dogs (with associated dose recommendations) are safer than the non-approved 'human' NSAIDs[4]. Some clinicians feel that certain NSAIDs may be associated with more adverse events than other NSAIDs, and case reports highlighting adverse events associated with particular NSAIDs probably fuels such opinions[5; 6]. However, there are no data comparing and contrasting the incidence of, or type of adverse events, associated with the different approved NSAIDs. Whether one particular NSAID is associated with a greater or lesser incidence of a particular side effect is unknown[3]. Clinicians should consider all the approved NSAIDs to all have the potential to be associated with side effects. NSAIDs can be associated with gastro-intestinal, renal and hepatic side effects[3; 4]. Although the side effects listed are associated with NSAIDs as a class, the appearance of side effects appear to be rather individual dog dependent. If side effects occur, clinicians often consider trying a different NSAID – this is probably the most common reason for switching between NSAIDs. The majority of this article will consider switching in the context of this scenario.

LACK OF EFFICACY

Varying individual response to NSAIDs in terms of efficacy is well recognized in humans[7; 8]. Clinically, it appears that individual dogs often respond better to particular NSAIDs, but there are no data documenting this in dogs except for the varying responses across individuals within a group that are seen in NSAID clinical trials of efficacy[9-11]. When a less than expected efficacy response is seen after 7-14 days of administering a NSAID, the recommendation is to try administering a different NSAID, and hence switching between NSAIDs. Although not well documented, analgesic efficacy of a given NSAID can seem to wane over time. This may be due to shifting neurobiology underlying pain. Interestingly, clinical experience, and some scientific data[12] suggests that switching from one NSAID to another can result in an apparent increase in efficacy from the NSAID analgesic. All NSAIDs have slightly different biological actions, including interacting with cannabinoid receptors, the vanilloid receptor TRPV1, NMDA and AMPA receptors[13-16]. The way a 'new' NSAID interacts with the shifted neurobiology driving pain may explain the apparent boost in efficacy. The varied and complex actions of NSAIDs also may explain the individual variability in analgesic response.

OTHER REASONS FOR SWITCHING

Other valid reasons for switching include owner preference (for whatever reason), and dosing difficulties.

OVERVIEW OF
CONCERNS AROUND SWITCHING

Concerns around switching between NSAIDs are focused on side effects – worries about drug overlap (pharmacokinetically or pharmacodynamically [with respect to adverse effects]) and the potential adverse effect on the patient.

WASHOUT PERIOD AND DRUG HALF LIVES

The currently available non-steroidal anti-inflammatory drugs (NSAIDs) for dogs are excreted at varying rates, depending on the metabolic pathway and extent of enterohepatic cycling. Although the drug distribution, half-life, and clearance, have been characterized for most NSAIDs used in animals, this information has not always been useful for predicting safe and effective dosage regimens. Half-lives of the NSAIDs approved for use in dogs do not correlate with the frequency of administration. Most currently-used oral NSAIDs are given once a day, but half-lives vary widely between commonly used UK products with values of 1.2 hours for robenacoxib, 1.38 hours for cimicoxib, 8 hours for firocoxib and carprofen, and 24 hours for meloxicam. Some people have recommended washout periods based on half-lives – suggesting 5 half-lives of the currently administered NSAID should be the length of the washout period. There is no evidence to support this recommendation.

An important feature of the NSAID pharmacokinetics is that anti-inflammatory and analgesic effects, and toxic effects, persist longer than the plasma half-lives predict[18]. One explanation for this disconnect between pharmacokinetics and pharmacodynamics is 'tissue selectivity'. Tissue selectivity occurs when the NSAID drug is cleared from the systemic circulation, but remains in the target inflamed tissues because of the acidic nature of the NSAID[19; 20]. Most NSAIDs approved for use in dogs are weak acids and also demonstrate this tissue selectivity. This is of benefit when considering inflammation and associated pain (e.g. post-operative wound inflammation; inflammation associated with OA), and prolonged presence of the NSAID in inflamed tissue following clearance from the systemic circulation has been demonstrated for several NSAIDs[21]. However, if an NSAID induces some gastrointestinal irritation, there may well be associated intestinal inflammation, and potentially a prolonged presence of drug in these tissues may occur. However, this latter comment is speculation. Regardless, tissue selectivity makes it more difficult to predict when a drug has completely been cleared from the system.

SWITCHING FROM ASPIRIN TO OTHER NSAIDS

Most experts agree that caution should be exercised when switching between treatment with aspirin and a cycloxygenase-2 (COX-2) selective drug. Aspirin is a non-selective COX inhibitor, and at low doses is more selective for COX-1. Aspirin has been associated with gastro-duodenal lesions in experimental dogs after oral administration, indeed aspirin administration is often used as a model of gastro-duodenal ulceration in dogs[22]. These lesions may be caused by two mechanisms – local effect on the stomach mucosa, and inhibition of COX-1. During treatment with aspirin a pathway is induced to produce lipoxin (lipoxin A4) also known as aspirin-triggered-lipoxin (ATL)[23]. Acetylation of the COX enzyme by aspirin blocks prostaglandin synthesis in both COX isoforms. However, aspirin-acetylated COX-2 can convert arachidonic acid to 15-R-hydroxyeicosatetraenoic acid (15-R-HETE), where subsequent metabolism occurs by 5-lipoxygenase to 15-epi-lipoxin $A_{4.}$ This aspirin-triggered-lipoxin (ATL) has a protective role, reducing inflammation.

Over time, gastrointestinal adaptation occurs – which is thought to be mediated by ATL – and induces the gastrointestinal mucosa to become more tolerant of potential injury caused by NSAIDs[24]. Such gastric adaption may involve other factors. However, when dogs received aspirin at a high dose of 25 mg/kg every 8 hours, there was no evidence of adaptation as the lesions were as severe or worse on day 28 compared to earlier in the study[25]. Upregulation of COX-2 after mucosal injury was demonstrated by Wooten et al[26] in which COX-2 was increased in the duodenum of dogs after administration of aspirin after 3 days.

It is plausible that treatment with a COX-2 inhibitor would suppress aspirin-induced induction of, and possibly the protection derived from, COX-2. Therefore, a washout time of several days (author recommends 7 days) between switching between a COX-2 inhibitor and aspirin seems appropriate. Additionally, caution should be exercised when administering aspirin simultaneously with COX- 1 sparing drugs.

OTHER SWITCHES

A question that is often asked is "should a washout time between other NSAID treatments also be recommended?" There are insufficient data to resolve this question and some conflicting evidence. A study by Dowers et al[27] suggests that some gastro-duodenal adaptation (that is, gastro-duodenal irritation occurs, but then subsides despite the continued administration of the NSAID) may occur after repeated administration of NSAIDs other than aspirin. In the Dowers study[27] the observed gastrointestinal lesions from administration of deracoxib and carprofen were worse early in the course of treatment to day 2, but were less (improving) by day 5. This may suggest that the time when dogs are more prone to injury from NSAIDs may occur early during the course of treatment – perhaps suggesting greater care with switching in this time period. There was also some evidence indicating that longer-term residual effects of NSAID treatment occurred in these experimental dogs. Lesions were observed even after a 16-day washout time. In another study, dogs with arthritis were treated every day for two months with carprofen[28]. Plasma proteins were lower at 4 weeks, but recovered to pre-treatment levels by 8 weeks. The protein loss may have been from changes in permeability of the gastrointestinal mucosa, suggesting again, that NSAID-induced risk of intestinal injury occurs early in the course of treatment. An interesting study by Goodman et al[29]. evaluated healing of endoscopically created gastro and duodenal ulcers when tepoxalin, firocoxib, or placebo were administered for 7 days in a randomized 3-way crossover study design. They concluded that COX-2 inhibition by firocoxib slowed wound healing by a mechanism independent of prostaglandin synthesis. This suggests caution when using selective COX-2 inhibitors in the face of gastro-intestinal lesions. A retrospective analysis of a clinical study of an NSAID treatment for OA-pain, evaluated dogs that did not complete the study[30]. Overall, reasons for not completing the study centered on adverse events. There was no difference in the number of dogs not completing the study when comparing dogs that had recently switched from another NSAID compared to those with no history of recent NSAID use[30]. Additionally, there was no difference in the number of dogs not completing the study when comparing various washout periods (up to 3 days; 4-5 days; 6-7 days) within dogs with a history of recent NSAID use[30]. A series of severe gastrointestinal lesions associated with the administration of a coxib non-steroidal were reported[31]. Most of the dogs in that report had received a high dose of the NSAID, or concurrent treatment with a corticosteroid, or had been switched from another NSAID to the studied coxib in close temporal association (e.g. rapid switching)[31]. The authors speculated that administering a COX-2 inhibitor to the dogs described in in this report shortly after another NSAID may have resulted in the ability for mucosal recovery, regeneration, and healing to have been compromised[31].

STUDY
RECOMMENDATIONS

Overall, the evidence supports a recommendation that if gastrointestinal injury or compromise is observed – or even suspected – administration of another NSAID before allowing for healing to occur, could produce additional injury. If switching because of adverse events such as vomiting, gastrointestinal injury should be assumed, and again, a 7-day washout period is recommended. Regardless, if switching from aspirin to another NSAID, especially a selective COX-2 inhibitor, a washout period of 7 days is recommended.

If switching between different COX-2 selective NSAIDs, or between COX-2 selective and non-selective NSAIDs (or vice versa), due to lack of efficacy, limited clinical data suggest that a washout period of just a few days (3) is appropriate.

ANALGESIC PROVISION DURING THE WASHOUT PERIOD

With switching, the question of 'what can I use to provide analgesia during the washout period?' comes up. In the chronic scenario, it is not known how long the residual analgesic effects remain after the last dose of chronic administration. However, clinically, it is clear that when an NSAID is stopped, there is not a sudden return to an untreated pain state at the time the next dose would have been due. Some dogs appear to return to a pain state more quickly than others, whereas other dogs appear to have residual analgesic effects lasting days to weeks. In the chronic scenario, each dog should be treated individually. Unfortunately, there are few proven analgesic options known to act quickly. Based on limited evidence, amantadine is thought to require several weeks to see an analgesic effect[32], and no work has been performed with gabapentin. *(The treatment options listed above may include off-label or off-cascade suggestions. Any decision on treatment protocols for a particular case remains the complete responsibility of the prescribing veterinary surgeon. In particular veterinary surgeons must be aware of relevant medicines legislation and whether it is legal to use certain treatments in their country of work).*

If clinicians are considering switching between NSAIDs perioperatively this could potentially present more of a problem in terms of pain perceived by the patient. **Switching from a 'perioperative' NSAID to a different NSAID to go home on, and subscribing to the idea of a washout period, could leave the patient without NSAID cover in the critical first few days postoperatively. For this reason, it is recommended not to switch between NSAIDs in the perioperative period**. If a dog is on a particular NSAID prior to surgery, or a dog receives an NSAID during surgery, then it is recommended to keep the dog on that NSAID during and after the surgery.

SUMMARY

Among the drugs available there may be variations among animals with respect to tolerance of adverse effects and clinical response. For both reasons of lack of analgesic response, and side effects, switching between NSAIDs is appropriate. When considering a switch from one NSAID to another for reasons of lack of efficacy of the first, the necessity of a washout period, discussed above, needs re-evaluation. Although the most conservative approach is to use a washout period of a few days, there is no scientific evidence that this is required, or any scientific evidence to inform what duration is appropriate. If switching between NSAIDs is being considered due to the gastrointestinal side effects, rapid switching to a drug that inhibits COX-2 could delay healing and possibly worsen the lesions. In this scenario, a washout period of 7 days is required. Switching between NSAIDs in the perioperative period is not recommended.

The information contained above is written based on the expertise and clinical experience of the author and is intended to provide additional material for consideration in the management of patients by the treating veterinary surgeon. Any decision on treatment protocols for a particular case remains the complete responsibility of the prescribing veterinary surgeon.

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+44 (0) 1280 814500 uk_office@vetoquinol.com www.vetoquinol.co.uk

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