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RESPONSIBLE NSAID USE

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Veterinary medicine has witnessed an explosive growth in the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Until the fall of 2002, we had 4 NSAIDs licensed for use in companion animals, yet we have seen 4 additional NSAIDs gain FDA registration within the past 24 months. Two of the more recently licensed NSAIDs are coxib-class NSAIDs and one is a ‘dual-pathway’ inhibitor.

The increased use of NSAIDs in veterinary medicine is paralleling that in human medicine. A recent report (Pain, 2004) cites the increased (human) use of NSAIDs from 1980 to 2000 for acute pain to have increased from 19% to 33%. Further, approximately 1/3 of all NSAID prescriptions in 2000 were for COX-2 inhibitors. This increased use of NSAIDs in both the human and veterinary sectors is likely influenced by 3 factors: 1) the World Health Organization (WHO) now suggests that all three categories of pain (mild, moderate and severe) be managed with the inclusion of an NSAID, 2) NSAIDs (especially COX-2 selective) have shown efficacy in the treatment of several types of cancer and 3) NSAIDs are high revenue items for both pharmaceutical companies and dispensing veterinarians.

The pharmacologic effects of this class of drugs include analgesia, antipyresis and control of inflammation. NSAIDs act to block the first step of prostaglandin synthesis by binding to and inhibiting cyclooxygenase. They also have direct inhibitory effects on neutrophils and are capable of immunomodulation. Physiological processes of NSAID analgesia include transduction, modulation and perception.

The ‘Achilles Heal’ of NSAIDs has historically been gastrointestinal damage, and dogs are described as a species particularly sensitive to NSAID gastric intolerance. Although not completely understood, several mechanisms have been proposed. Gastroduodenal erosion and ulceration reflects inhibition of prostaglandin E2 mediated bicarbonate and mucus secretion, epithelialization and fluid flow. Salicylates have long been recognized as causing injury to mucosal cells and submucosal capillaries, even at low doses. Yet there is no apparent chemical characteristic which can be used to predict the likelihood of gastrointestinal toxicity by a particular NSAID. Further, NSAIDs in the same chemical class (such as ibuprofen and carprofen, deracoxib and firocoxib) typically demonstrate very different pharmacokinetic profiles and physiologic effects.

In 1970 Vane and others discovered that the mode of action for aspirin lay in its interaction with the enzyme cyclooxygenase converting arachidonic acid to the eicosanoid prostaglandins. Twenty years later cyclooxygenase was recognized to reflect an actual family of enzymes. In most simplistic terms, COX-1 exists in relatively high systemic concentrations and ensures homeostasis of the GI tract, platelet aggregation and renal GFR. It is, therefore, referred to as the constitutive cyclooxygenase isozyme. In contrast, COX-2 is in relative low systemic concentrations excepting in a state of inflammation, where it is considerably up-regulated. It is therefore recognized as the inducible isozyme. Following this differentiation, the pharmaceutical companies identified the potential value of developing a drug specific for the COX-2 (bad) isozyme that ‘spares’ the COX-1 (good) isozyme. Hence, the introduction of celecoxib (Celebrex®) and thereafter rofecoxib (Vioxx®). However, further developments in NSAID research has revealed that this is a naive approach in that COX-2 is recognized as essential for some renal function in man and dogs, required for female reproduction, and is found in the CNS. Accordingly, there are negative consequences for being “too COX-2 selective.” In addition, since both COX-1 and COX-2 are constitutive for renal function, the new coxib NSAIDs are neither more or less safe to the kidney than traditional NSAIDs.

The amount of drug necessary to inhibit each of the two cyclooxygenase isoforms provides a basis for assessing relative safety and efficacy of each NSAID. The measurement of thromboxane B2 synthesis from platelets, which constitutively express COX-1 following blood coagulation is a specific test for COX-1 activity. Measurement of prostaglandin E2 production from monocytes and macrophages in whole blood following stimulation with lipopolysaccharide is a specific test for COX-2 activity. The COX-1 : COX-2 ratio then offers some insight as to the differential pharmacologic and toxic effect of the NSAID. A ratio greater than 1 indicates that the drug is more potent toward COX-2, thereby suggesting a safer drug compared to a drug characterized by a ratio less than one. Nevertheless, clinical relevance of this ratio is undetermined, in that there is surely a ratio (as yet unknown) at which detrimental effects will prevail. COX-1 : COX-2 ratios range from aspirin (<0.3) to deracoxib (1275) [reported values may vary depending upon assay methods, animal species, laboratory techniques, etc.]. The coxib class NSAIDs, which are reported to have a favorable safety profile, demonstrate their COX-2 selectivity within a given dosage range. Coxib class NSAIDs can be forced out of their selectivity window by overdosing.

One might expect that the ‘newer’ the NSAID, the better the efficacy and safety; however, this is not necessarily true. Comparative NSAID safety is exceedingly difficult to assess. Most NSAID adverse drug events (ADEs) reported to the FDA are reported by the drug manufacturer. Yet reporting standards are not uniform amongst the manufacturers. Increasingly, clients challenge their veterinarian on comparative data obtained from the internet, where they wish to compare the incidence of ADEs between 2 NSAIDs. The actual number of dogs showing an ADE is impossible to determine since not all problems are reported and not all reported problems are definitively related solely to the administered NSAID. And, the actual number of dogs taking a given NSAID at a given time is unknown. Therefore, when comparing the incidence of ADEs between 2 NSAIDs, where the numerator is unknown for either drug and the denominator is also unknown for either drug, any meaningful conclusion is elusive.

Not withstanding their anticipated ‘safer’ profile, even the new coxib class NSAIDs are associated with ADEs. These events fall into 3 categories: 1) inherent drug toxicity, 2) inappropriate veterinary administration, and 3) pet owner ignorance. For reasons unknown, some individual animals are ill-tolerant of some NSAIDs. For all NSAIDs organ systems most often affected, in decreasing frequency, are GI tract, kidney and liver. Inappropriate veterinary administration includes: poor NSAID candidate selection based on compromised physiologic systems, overdosing, concurrent use with other NSAIDs and/or corticosteroids, dosing errors based on kilogram to pound conversion, failure to ask the owner if their pet is on any other ‘aspirin-like’
product (often owners do not consider aspirin products as drugs), failure to send home client information and inattention to follow up after administering NSAIDs. Client ignorance includes noncompliance, naivety in administering over the counter NSAIDs in addition to a prescription NSAID and failure to notify their veterinarian at the first clinical signs of intolerance.

For example: 28% of all reported deracoxib ADEs, regardless of the organ system involved, for the first 18 months of use were in dogs given concurrent NSAIDs or corticosteroids. This is an alarming figure, especially considering that every contemporary NSAID label cautions the use of a concurrent NSAID and/or corticosteroid! Dogs with noteworthy preexisting disease and given concurrent NSAIDs and/or corticosteroids constituted 67% of the ADE reports! These data suggest appropriate patient selection and responsible prescribing of NSAIDs can be improved upon within the veterinary clinic. However, there may be an additional underlying factor.

Although not licensed for use in dogs, aspirin is widely used. It is relatively inexpensive and easy to obtain, existing in many household medicine cabinets. Most consumers consider aspirin a benign product and do not consider it a drug. After all, television ads suggest you should take aspirin daily so as to minimize your risks with a heart attack. As a society we have become quite cavalier about 'aspirin' use, yet the AMA reported 16,500 human deaths in 2000 directly related to aspirin use. When prescribing any contemporary NSAID we should ask the pet owner if they are administering any other aspirin-like product to their dog as part of the medical history. When asked if they are administering any other NSAID or drugs to their dog, they often say no, either because they do not know what an NSAID is or they do not consider aspirin (or other over the counter products) as drugs (just as they fail to recognize flea and heartworm products are also drugs).

For years we have known that salicylates cause petechiation and hemorrhage of the GI tract. Toxicity is recognized both systemically and at the level of the gastric mucosa. Until recently the systemic toxicity has not been well defined, but local damage has long been attributed to 'back diffusion' of acid which causes injury to mucosal cells and submucosal capillaries. Aspirin Triggering Lipoxin (ATL) has recently been identified which provides a hypothesis for systemic salicylate toxicity as well as GI damage when concurrent NSAIDs are used (TRENDS, 2003).

With ubiquitous cell degradation, arachidonic acid is released. This arachidonic acid is then metabolized in the reticulocyte via the 15(R)-HETE pathway to ATL. ATL serves an anti-inflammatory role and decreases PMN recruitment, i.e., serves a protective role. (This PMN recruitment is speculated to be part of the mechanism behind systemic salicylate toxicity.) This pathway is blocked with the addition of a second NSAID, giving rise to an alternative metabolic pathway (in the PMN) yielding LTB4. LTB4 is a strong chemotactic factor, enhancing leukocyte adherence to gastric microcirculation. So, when the dog owner supplements your prescription NSAID with over-the-counter aspirin (anticipating increased pet activity from weekend-warrior activities) s/he is actually blocking the protective ATL phenomena, and accentuating the potential for gastric injury. It is our veterinary responsibility to inform pet owners of this potential problem.

The obvious question is how long a washout period should follow aspirin before the administration of a different NSAID. This question begs further research; however, most suggest a washout period of 10-14 days following aspirin. This suggested washout period takes into consideration platelet replacement time, since platelets are irreversibly acetylated with aspirin.

Hellyer et al (2004 ACVA) have investigated the washout period for administration of deracoxib following carprofen and found that there are no apparent concerns in healthy dogs when making this change at the next 24 hour dosing interval. Barring the ATL issue, which is unique to aspirin, and insight provided by Hellyer’s study of deracoxib following carprofen, there is virtually no evidence-based guidance for washout periods with the multiple permutations possible with all the various NSAIDs. Therefore, a rule of thumb for washout is 5-10 half-lives following the first NSAID.

Ultimately, the key to responsible use of NSAIDs, which is potentially one of the most valuable class of drugs available for veterinary use, is appropriate client selection, education of both the veterinary staff and pet owner and patient follow up.