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Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used analgesics in veterinary medicine. They are crucial for the treatment of acute and chronic pain in dogs and cats. In the acute pain scenario, as in the perioperative period, NSAIDs are usually used as part of a multimodal treatment. The latter is preferred as it refers to the concomitant use of 2 or more classes of analgesics, which results in reduction of doses, synergistic effects, as well as reduced morbidity and mortality. In the chronic pain scenario, as in osteoarthrosis, NSAIDs are the first line of pharmacological treatment, and are usually associated with other analgesics or non-pharmacological treatments such as weight control, physical activity, environmental changes, among others.[1]

The anti-inflammatory and analgesic effects of NSAIDs are related to the inhibition of the expression of cyclooxygenase (COX) enzymes in cell membranes. In a simple approach, it is well accepted that COX-1 enzymes are generally related to constitutive functions of cells which maintain homeostasis, whereas COX-2 enzymes are generally induced after tissue injury in order to produce inflammatory mediators that amplify nociceptive input (pain) to the spinal cord. Therefore, most of NSAIDs´ analgesic effects are related to the depression of COX-2 induced-effects, and most of the adverse-effects are related to the depression of COX-1 cytoprotective effects.[2,3]

In the gastrointestinal tract, inhibition of COX-1 will result in decreased secretion of gastric mucous and bicarbonate and decreased mucosal blood flow. This results in irritation of the gastric mucosa which can progress to ulceration and perforation.[4] In humans, NSAIDs that are COX-2 selective or preferential are known to be safer for the GI tract.

In the hematopoietic system, COX-1 inhibition affects platelet aggregation by decreased production of thromboxane and consequent decreased platelet aggregation and vasoconstriction. Aspirin is particular as it irreversibly affects platelet-aggregation.

In the kidneys, the adverse-effects are related with the inhibition of both COX isoforms, which affects the maintenance of the renal perfusion (vasodilation of the renal artery) in conditions of hypotension or hypovolemia.

There is also hepatic adverse-effects which are not related to the inhibition of COX enzymes, but rather, are considered as an idiosyncratic effect of the drug (i.e., are unpredictable, are not dose-dependent and are not consistently inducible).

The true incidence of NSAIDs-related adverse-effects remains unknown. The most common adverse-effects of NSAIDs are gastrointestinal signs (vomiting, diarrhoea and anorexia). These are generally self-limiting or require minimal supportive treatment such as gastroprotectants (famotidine, omeprazole) and sucralfate, anti-nausea medications (metoclopramide, ondansetron, maropitant) ± fluid therapy. If the clinical signs are not initially detected, adverse-effects may potentially progress to gastrointestinal ulceration and perforation, leading to septic abdomen and shock, renal or liver failure, or prolongation of bleeding times. In these circumstances, they require emergency treatment and prognosis can be reserved or poor.

A systematic review of studies in which dogs were administered NSAIDs concluded that the overall incidence of adverse drug experiences cannot be calculated from the data in the literature. Nevertheless, estimates for the most serious adverse effects suggest that they occur at a very low frequency, and are usually related with erroneous administration of these

drugs.[4] Furthermore, a retrospective study looking at gastrointestinal perforation following NSAID treatment also revealed that 90% of the cases had some error in the administration.[5] Risk factors for the development of serious adverse-effects may include the administration "off-label," at higher doses than recommended, for prolonged periods of time, or in combination with corticosteroids or a 2nd NSAID.

Guidelines to prevent the development of serious adverse-effects following NSAID administration are available.[2] Patients should be carefully selected including screening for pre-existing diseases, current medications and possible drug interactions. Good client communication is imperative. Owners should be educated to identify potential adverse-effects and take the necessary measures in case they develop.

A hand-out explaining about NSAIDs and potential adverse-effects can be given to owners and may help the veterinarian in terms of liability. Continued monitoring including recheck consults, follow-up by telephone and monitoring of liver and renal enzymes are also recommended. Fluidtherapy and monitoring of blood pressure should be performed during surgical procedures in which NSAIDs were administered pre-emptively (i.e., before the painful stimulus). A minimum wash-out period of 5–7 days is recommended when switching NSAIDs.[2]

Only veterinary-approved NSAIDs should be used in animals and label recommendations should be respected. Ibuprofen has a narrow margin of safety and is the most common drug involved in drug exposure to dogs and cats that is reported to the American Society for Prevention of Cruelty to Animals.[6] Paracetamol (or acetaminophen) is toxic in cats. Veterinarians are encouraged to report adverse-effects to the pharmacovigilance service of drug companies. This will reinforce post-marketing and safety data as well as provide evidence for the development of safer NSAIDs.

The following are contra-indications for the use of NSAIDs: History of gastrointestinal disease, history of NSAID intolerance, preexisting renal or hepatic disease, anemia, coagulopathies, hypovolemia or hypotension, concurrent corticosteroid use (including topical treatments) and administration in close temporal relationship with other NSAIDs. In general, NSAID administration will be contraindicated in most ICU (intensive care unit) patients.

Cats have some particularities due to limited hepatic glucuronidation and potential greater incidence of adverse-effects.[7] However, NSAIDs that are labelled for use in cats have recently entered the veterinary market, and these seem to have good efficacy and safety even for long term administration. Additionally, although NSAIDs would be normally contra-indicated in renal patients, recent research is indicating otherwise.[8,9]

Based on available evidence, it seems that meloxicam and robenacoxib can be safely administered to cats with concomitant chronic painful conditions and chronic kidney disease.

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