Case report #1

Use of NSAIDs in a female dog with a mammary tumour

1433 Words

Introduction

An intact, 16-year old, female dog was diagnosed with a large and metastatic mammary tumour. As surgery and cancer chemotherapy were unadvised for this case, a palliative treatment was suggested with a preference for a non-steroidal anti-inflammatory drug (NSAID). The use of a selective COX-2 inhibitor will be discussed.

Problem list

- Benefit of NSAIDs for management of cancer pain
- Benefit of NSAIDs in cancer chemoprevention and treatment
- Toxicity of NSAIDs (selective versus non-selective COX-2 inhibitors)
- Choice of a selective COX-2 inhibitor (pharmacokinetic considerations)

NSAIDs for management of cancer pain

In dogs, NSAIDs are used widely to control acute and chronic pain of the musculoskeletal system (Bergh & Budsberg, 2005). However, mild to moderate cancer pain, especially that which arises from intrathoracic masses, intra-abdominal masses, bone tumours and metastases, can also be relieved in dogs with NSAIDs (Gaynor, 2008). The female dog, here, was not fully investigated for pain but to begin the management of its pain with NSAIDs could be reasonable as a first choice palliative treatment. If the pain is then not sufficiently reduced or is estimated as severe, opioids like buprenorphine, licensed for use in dogs, could be added to the NSAID treatment. Indeed, NSAIDs have an opioid-sparing effect such that better analgesia can be achieved with lower doses of opioids (Gaynor, 2008).

Choosing between the different NSAIDs available based on their analgesic properties is quite difficult since no clinical study has been carried out for cancer pain management. The different existing models used to assess pain relief with NSAIDs are lameness associated with synovitis, surgery or inflammation and these models are not able to discriminate clearly between different agents. For example, meloxicam and carprofen administered preoperatively to dogs undergoing orthopaedic

surgery were similarly effective in relieving the signs of pain for up to 24 hours in all of the dogs (Laredo, Belda et al., 2004). The studies carried with newer NSAID (robenacoxib, firocoxib) which are selective cyclooxygenase-2 (COX-2) inhibitors, have shown similar or slightly increased efficacy compared to non-selective NSAIDs (Schmid, Spreng et al., 2009; Gruet, Seewald et al., 2011). Consequently, the analgesic effects of different NSAIDs administered at the recommended dosages can neither obviously direct the choice between selective versus non-selective COX-2 inhibitors nor between the different licensed drugs.

NSAIDs in cancer chemoprevention and treatment

NSAIDs are not licensed for cancer control but were first recognized for their potential anticancer activity after comparing cancer incidence in individuals who did and did not routinely use these agents. NSAIDs were shown to be chemopreventive for colorectal cancer in humans (Baek, McEntee et al., 2009). In dogs with inflammatory mammary carcinoma, piroxicam resulted in remission in 12 of 18 cases (de, Toledo-Piza et al., 2009). The effect of deracoxib was also assessed in invasive transitional cell carcinoma of the urinary bladder and for 24 dogs, partial remission or stable disease were observed in 4 and 17 dogs respectively (McMillan, Boria et al., 2011). The chemopreventive action of NSAIDs could be related to the inhibition of COX-2 and reduction of prostaglandin synthesis. COX-2 has been demonstrated as tumorigen in knock-out mice and PGE_2 was shown to be a protumorigenic agent (Baek, McEntee et al., 2009). In dogs, the involvement of COX-2 as a cancer promoter has been described in several studies (Queiroga, Perez-Alenza et al., 2005; Lavalle, Bertagnolli et al., 2009; Queiroga, Pires et al., 2010). COX-2 was overexpressed in several tumour tissues (prostate, ovary, bladder, intestine, mammary gland and nasal cavity) and was associated with higher microvessel density, promotion of angiogenesis and poor prognosis. COX-1 and 5-lipoxygenase (5-LOX) were less studied but could also be targeted for the prevention of cancer (Baek, McEntee et al., 2009). Additional modes of action of NSAIDs on tumours, other than inhibition of COX and 5-LOX, have also been suggested, such as the activation of several genes like NAG-1 (NSAID-activated gene 1) and EGR-1 (early growth response-1), which are tumour suppressor genes. However, since COX-2 inhibition was described at the time as being the main mode of action of NSAID in cancer prevention, a selective COX-2 inhibitor would be preferred in this dog for tumour growth management. Studies comparing the different selective COX-2 inhibitors in veterinary medicine in their ability to control cancer are lacking and there are only two studies looking at selective COX-2 inhibitors in the treatment of transitional cell and mammary carcinoma carried out with doracoxib and piroxicam (not a true selective COX-2 inhibitor). Selective COX-2 inhibitors available include mavacoxib, cimicoxib, firocoxib and robenacoxib. These have the same target and we could assume that the outcomes could be similar to doracoxib.

Toxicity of NSAIDs (selective versus non-selective COX-2 inhibitors)

NSAIDs approved for use in dogs have few side effects, most commonly, vomiting, diarrhoea, and inappetence. Other less common side effects include gastrointestinal ulceration, renal failure and

hepatic dysfunction. Drugs with preferential activity on COX-2 have provided a major advance in pain therapy since, although not universally accepted, selective COX-2 inhibitors have improved gastrointestinal tolerance and potentially fewer renal effects. These selective drugs should be considered a priority in animals that have cancer as these cases are often old and potentially have reduced renal function or even chronic renal failure. Moreover, in parallel to the NSAID cancer cases could be receiving chemotherapy that may induce thrombocytopenia and increase putative gastrointestinal bleeding. In this case, the dog had no additional therapy but had a poor health status which could have deteriorate further is adverse effects occurred.

The reduction of adverse effects combined with the selective activity on COX-2 potentially involved in tumour growth supports the use of a selective COX-2 inhibitor in this dog. In the two studies on the potential utility of a selective COX-2 inhibitor in the treatment of transitional cell or mammary carcinoma in dogs with mean ages of 10 to 11 years old showed that two (6%) dogs on piroxicam had to discontinue treatment, whereas no dog had to stop treatment with deracoxib, even if gastrointestinal signs were observed, since the clinical signs related to adverse effects were mild (de, Toledo-Piza et al., 2009; McMillan, Boria et al., 2011). As deracoxib appeared to have few adverse effects, mavacoxib, firocoxib, cimicoxib or robenacoxib, which have same mode of action, could be prescribed for this dog.

Choice of a selective COX-2 inhibitor (pharmacokinetic considerations)

The greatest difference between the selective COX-2 inhibitors is their different pharmacokinetic properties. Firocoxib, robenacoxib and cimicoxib have quite short half-lives of 6, 0.7 and 1.4 hours, respectively, and must be administered once a day in dogs to maintain analgesic effects (McCann, Andersen et al., 2004; Schmid, Spreng et al., 2009). These short half-lives imply short duration of effect. Indeed, analgesic effects were only proved for 12 hours for firocoxib and robenacoxib (published data for cimicoxib in dogs is lacking). After 12 hours, data is lacking and it is not clear whether the analgesic effects would remain throughout the 24-h dosing interval. In contrast to these drugs, mavacoxib has an extremely long half-life (mean of 21 days) inducing analgesic effects that would remain all day long between the monthly recommended administrations (Cox, Liao et al., 2010).

If we assume that the pain associated with cancer is felt all day, a NSAID with a long half-life, mavacoxib, would be preferred. However adverse effects, which are lower for selective than for non-selective COX-2 inhibitors, cannot be excluded and if they occur it is impossible to rapidly reverse the clinical signs by suspending the treatment with mavacoxib as the effects persist for several weeks after a single dose. As this dog already had a poor health status, anything more than an acute adverse effect could not be tolerated and the use of mavacoxib was not advised. A selective COX-2 inhibitor with a short half-life wold be the most appropriate option for this dog and firocoxib was chosen arbitrarily.

Conclusion

A NSAID could be of interest for this cancer dog as a palliative agent to relieve pain. For cancer control in the dog, even if some *in vitro* or clinical studies in some types of cancer showed a benefit, more clinical studies on the efficacy of NSAIDs on mammary tumours should be carried out to prove the beneficial effects. In this case, among NSAIDs, selective COX-2 inhibitors, which are known to have fewer adverse effects, would be preferred. A drug with a short half-life would allow a rapid withdrawal of the drug if any clinical signs of adverse effects occurred. So, firocoxib was prescribed for this dog. If the pain relief provided by with firocoxib was insufficient, another analgesic drug, such as buprenorphine, could be added to the therapy.

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