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VETERINARY PAIN MANAGEMENT

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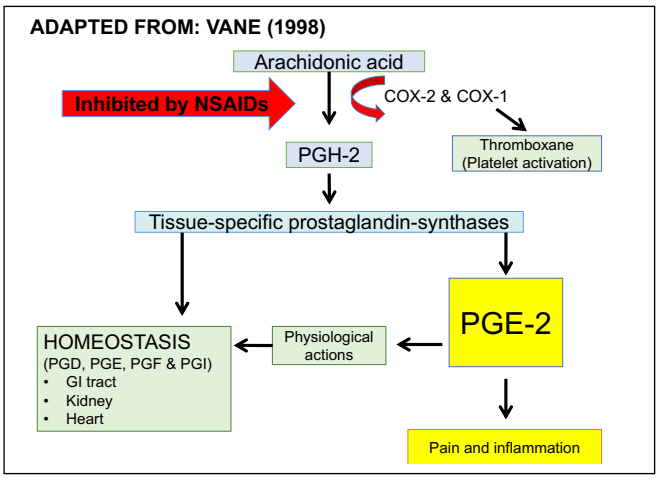
Pharmacology of pain: NSAIDs

Key points:

1. **COX-2 selectivity does not confer increased safety, or greater efficacy.**
2. **No current NSAID consistently shows greater pain-relieving efficacy.**
3. **Daily dosing for OA-related pain may be better than dosing 'as required', improving QoL.**
4. **NSAID efficacy is unrelated to ongoing plasma levels.**
5. **NSAID-related hepatopathy is idiosyncratic.**
6. ***"There is no information on the safety of … using topical corticosteroids with NSAID".***
7. **Pharmacogenetics can affect metabolism & efficacy of NSAID within and between dog breeds.**

1. COX-1:COX-2 selectivity

- Both COX-1 and COX-2 pathways produce PGs with constitutive, physiological effects [39-41, 44].
- Both pathways produce PGE2 [20].
- PGE2 has physiological functions, but also mediates pain and inflammation [37].
- COX-2 is markedly induced during inflammation, presenting a therapeutic target [35].
- No NSAID consistently shows greater efficacy or safety [8, 20, 21, 30].
- Increased COX-2 selectivity of NSAIDs does not confer greater safety (GI, kidney or liver) [16, 28].
- COX-2 aids healing of GI ulcers [20].



2. Dosing NSAIDs - daily or 'as required'?

- A reducing dose of NSAID maintained the mobility of approx. 57% of dogs with OA, but there was no means of predicting these individuals [43].
- Owners may not recognise subtle behavioural signs of pain, especially with bilateral lameness [1, 26, 27, 29].
- Unrecognised long-term pain predisposes to central sensitisation, increasing the pain experience [7, 18].
- The clinical relevance of *in vitro* NSAID effects on chondrocyte health remains controversial [6, 28].
- Evidence supporting long-term (>28d) NSAID therapy in dogs may be summarised:
  - Reduces pain & increases weightbearing in affected limbs [14],
  - Improves health related quality of life for dogs [34],
  - Long-term use does not increase the risk of NSAID-related adverse effects [17],
- **Cats:** Meloxicam and robenacoxib are licensed for long-term use in cats in the UK.

3. Reducing the risk of NSAID-related adverse effects. See Kukanich et al (2012) & Murrell (2018)

Data sheets state NSAIDs are contraindicated in animals with several comorbidities. Pragmatic discussions about the risks and benefits are required with the owners of these animals, before obtaining informed consent for NSAID use.

3.1 Liver disease

- NSAID-related hepatopathy may be overdose-related toxicity[20], or an idiosyncratic effect involving "*mitochondrial injury, oxido-reductive stress & altered hepatobiliary*" - see **Boelsterli (2013)**[5]. Marginally elevated liver enzymes do not necessarily predict susceptibility to NSAID-related hepatopathy [20].
- Hepatic fibrosis may predispose to GI ulceration [12], hepatopathy reduces metabolism of some NSAIDs [20, 24].
- *"Check liver function (BAST) if liver enzymes rising, ALT >2x upper range, or ALKP >5x upper range"* [21].

3.2 Kidney disease

- When renal blood flow is reduced COX-mediated production of PGE2 reduces renal vascular resistance, as a compensatory mechanism to maintain perfusion of the kidney [20].
- NSAID-related kidney toxicity follows overdose or administration during hypotension (e.g. dehydration, shock, hyponatraemia, cardiogenic).

- During GA measures should be taken to maintain mean arterial pressure >60mmHg, to preserve kidney perfusion. [20, 28].
- Blood flow in diseased kidneys is maintained by increased COX-2 expression, NSAIDs could cause an acute decompensation of kidney perfusion and decreased renal function [20]. Renal disease should be staged using IRIS parameters. Decisions whether to administer NSAID to a dog with pre-existing kidney disease depend on individual circumstances, should be undertaken with caution and require owners' informed consent.
- Renal function in cats with **stable** IRIS Grade 1 or 2/IV CRF was unaffected by long-term treatment with meloxicam [15].

3.3 NSAID & concurrent medicines

- **3.3.1 Ear preparations containing corticosteroids** suppress HPA function after 7 days' topical application to the ear canal[33]. This may increase the risk of GI adverse effects when combined with NSAID and "*there is no information on the safety … of using topical corticosteroids with NSAID*" [21].
- **3.3.2 Tramadol.** Dosing tramadol with NSAIDs may increase the risk of GI adverse effects [19-21].
- **3.3.3 Cyclosporin (CSA).** Co-administration of CSA and NSAIDs can potentially impair renal function and reduce myocardial contractility [10]. **Veterinary relevance: unclear**.

3.4 NSAID efficacy is not related to ongoing plasma levels of drug.

- NSAIDs are weak acids, becoming non-ionised and less able to cross cell membranes in low pH tissue (e.g. after inflammation), or *"ion-trapping"* – see **Ellis & Blake (1993**) *[11].* NSAIDS accumulate in inflamed tissue, maintaining local efficacy after blood levels fall.

Drug Name	$t_{1/2}$ in dogs
Carprofen	5-9 hrs
Cimicoxib	1.4 hrs
Firocoxib	6-9 hrs
Mavacoxib	30-40 days*
Meloxicam	24 hrs
Robenacoxib	1.2 hrs

4. NSAID - Why consider changing drug?

- Changing NSAID may improve management of OA-related pain [22].
- NSAID metabolism in dogs varies within[31] and between breeds [9 13]. NSAID metabolism was also reduced dogs with OA-related inflammation[38]. People show polymorphism in COX-2 [23] and PGE2 receptor (EP4) [4], both of which may affect the efficacy of NSAID. These polymorphisms have not been demonstrated in cats or dogs.
- If changing NSAID choose a drug from different subclass: **Propionic acid (**carprofen), or **Oxicam (**meloxicam), or **COXIBs (**cimicoxib, firocoxib, robenacoxib, or mavacoxib).
- Observe a suitable 'wash-out' period of 4-5 times t/2 between drugs - see **Kukanich et al (2012)** [20].

5. Do NSAIDs inhibit bone healing?

- Prostaglandins are involved in pain and also have paracrine and autocrine effects on non-neural tissues, e.g. PGE2 facilitates osteolysis and osteogenesis. Although preclinical work suggests NSAID may inhibit bone healing clinical relevance remains unclear, as there is no epidemic of fracture repair failures.
- **Barry (2010)** reviewed the veterinary field – the paper is freely available on Google Scholar. The author notes the difficulty in assessing the clinical effect of NSAID on bone healing and noting a variety of factors affecting surgical success, including '*vascularity, infection, expertise in fracture repair and stabilisation, fracture gap, debris, co-administered drugs and concurrent disease(s) affecting bone health* [3].
- **Marquez-Lara (2016)** reviewed the human field, noting:
  - poor quality research tended to show NSAIDs inhibited fracture healing,
  - higher quality research showed NSAIDs did not affect fracture healing [25].
- There is a need for high quality prospective studies to provide sound clinical evidence.
- **Veterinary relevance: Marquez- Lara (2016) and Murrell (2018)** conclude there is insufficient clinical evidence to withhold NSAIDs from patients undergoing orthopaedic surgery [25, 28].

6. NSAIDs and heart disease

- **Forward failure.** Decompensated heart failure reduces effective renal blood flow. NSAID administration may prevent the PGE2-mediated compensatory mechanisms to restore renal perfusion - see 3.2 above and Pouchelon et al (2015) [32].
- **Anti-diuresis.** NSAID inhibition of PGE2 increases Na-K-2Cl cotransporter expression in the ascending Loop of Henle [36]. In people this causes Na/water retention & may precipitate congestive heart failure in susceptible individuals [2]. **Veterinary relevance: unclear** [28]
- **Pro-thrombotic effect.** COX-1 mediates production of thromboxane-2, increasing platelet aggregation, whereas COX-2 mediates production of PGI2 (prostacyclin), limiting coagulation. People dosed with COXIBs showed a pro-thrombotic state, increasing risks of infarct (brain or heart) [42]. **Veterinary relevance: unclear** [28].

References available on request **January 2019**