CAPSULE REVIEW

Long-term use of non-steroidal anti-inflammatory drugs in cats with chronic kidney disease: from controversy to optimism

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This is the first of a series of *capsule reviews* published by the World Small Animal Veterinary Association - Global Pain Council (WSAVA-GPC). Each of these short articles provides a brisk assessment of the scientific evidence in specific aspects of pain management, including analgesic techniques, recommendations and controversies surrounding their use. In this first *capsule review*, the scientific evidence available on the long-term use of non-steroidal anti-inflammatory drugs in cats with concomitant chronic pain and chronic kidney disease is discussed.

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are excellent analgesics when administered as a single agent or as a component of multimodal treatment along with other pharmacological and non-pharmacological therapies (Mathews *et al.* 2014). These drugs are the mainstay of treatment of several long-term painful conditions that are caused, at least in part, by inflammation. Nevertheless, they have narrow safety margins and can cause adverse effects, including gastrointestinal, hepatic, renal and coagulation disorders (Monteiro-Steagall *et al.* 2013).

In cats, chronic kidney disease (CKD) is common and has an unclear aetiology (Marino *et al.* 2014, Sparkes *et al.* 2016). Its prevalence increases with age and can affect up to 40% of cats over 10 years of age and 80% of cats older than 15 years of age (Marino *et al.* 2014). Osteoarthritis (OA) is the most common chronic painful condition in cats. Radiographic evidence of OA has been reported in as many as 61% of cats older than 6 years and in up to 90% of cats aged >12 years (Hardie *et al.* 2002, Lascelles *et al.* 2010, Slingerland *et al.* 2011). Other chronic painful conditions (such as cancer and periodontal disease) are also common in older cats. Painful conditions and CKD often coexist in our feline patients, and providing pain relief becomes a challenge because of the fear of NSAID-associated adverse effects. However, without treatment of pain, there are negative effects on welfare and quality of life.

CKD may coexist with OA in almost 70% of cats (Marino *et al.* 2014), yet NSAIDs have historically been believed to be contraindicated in cats with renal disease (Lascelles *et al.* 2005). Recent publications have challenged this belief and suggest that NSAIDs can, with care, be administered to cats with CKD. This *Capsule review* presents the current evidence and recommendations on the long-term use of NSAIDs in cats with CKD.

RATIONALE

NSAIDs inhibit the expression of cyclooxygenase (COX) enzymes in cell membranes. These enzymes are essential for the biosynthesis

JSAP JOURNAL OF SMALL ANIMAL PRACTICE

of prostaglandins responsible for various biological functions and homeostasis. There are at least two COX isoforms (COX-1 and COX-2). Inhibition of prostaglandin production occurs to different extents depending on the COX selectivity of each NSAID. Both COX-1 and COX-2 are constitutively expressed in the kidneys, and their metabolites are important mediators for the maintenance of renal perfusion and auto-regulation. Prostaglandins such as PGE2 and PGI2 promote vasodilation and inhibition of Na^+ reabsorption, while thromboxane A2 modulates renin production and vasoconstriction (Rios *et al.* 2012, Curiel & Katz 2013). These mechanisms are particularly important in protecting normal kidney function during periods of dehydration and hypovolaemia (Cheng & Harris 2005). Thus, it has been speculated that prostaglandin inhibition after the administration of NSAIDs could result in deleterious renal effects in susceptible patients (Rios *et al.* 2012). Cats with pre-existing CKD could be at increased risk of renal toxicity associated with NSAID administration. Nevertheless, it is not clear how decreases in renal blood flow are associated with acute renal damage.

CONTROVERSY *VERSUS* EVIDENCE

Despite the concerns outlined above, long-term NSAID therapy was found to be safe and efficacious when administered to cats with OA (mean age: 12.9 years old) for approximately 6 months (Gunew *et al.* 2008). In this prospective study, no difference in serum creatinine levels were found between cats treated with meloxicam or placebo (n=40 cats per group). Following their findings, investigators set out to discover if the previously reported safety profile of NSAIDs would be reproducible in cats with CKD. Results from two additional retrospective studies with meloxicam and one prospective study with robenacoxib indicate that NSAIDs can be safely administered to cats with stable CKD.

However, the definition of "stable" CKD is not clear in previous publications. Some authors defined stable CKD as minimal changes in bodyweight and creatinine over time (less than 10 to 15% during 1 to 2 months), as well as controlled concurrent conditions such as hypertension, urinary tract infections and periodontal disease (Gowan *et al.* 2011, 2012). Other authors have considered changes in plasma creatinine concentrations greater than 25% over 1 to 2 months consistent with unstable CKD (Geddes *et al.* 2013). Table 1 provides specific details of these studies, including dosage regimens. In brief, based on serum creatinine and urea nitrogen concentrations plus urine concentration ability, NSAID-associated renal adverse effects were not detected in cats with CKD following meloxicam (Gowan *et al.* 2011) or robenacoxib (King *et al.* 2016) administration. In addition, the longevity of cats with CKD does not seem to be affected by the long-term administration of NSAIDs (Gowan *et al.* 2012). Increases in serum creatinine concentrations were reported to be slower in cats with CKD treated with meloxicam than in cats with CKD that did not receive meloxicam (Gowan *et al.* 2011). The authors hypothesised that improved mobility and overall quality of life subsequent to pain relief may have resulted in better appetite and increased water consumption. An alternative hypothesis was that the NSAID had a direct anti-inflammatory effect on the kidneys and consequent abrogation of renal functional deterioration over time (Gowan *et al.* 2011). A lack of NSAID-related adverse effects was also reported in induced kidney failure: six healthy cats with surgically induced CKD [International Renal Interest Society (IRIS) stages 2 and 3] were administered doses of 0.2 mg/kg meloxicam subcutaneously (sc), on day 1; 0.1 mg/kg meloxicam, sc afterwards, 20 mg/kg acetylsalicylic acid orally on days 1, 4 and 7 or placebo for 7 days in a crossover study. Despite the ethical concerns of such studies, no difference was found between the groups based on the urinary clearance of exogenously administered creatinine, serum creatinine concentration or urine protein-to-creatinine concentration ratio (Surdyk *et al.* 2013).

In humans, there is similar controversy. In a systematic review including nearly 12,500 individuals receiving NSAIDs and 23,900 controls, eight of nine studies failed to identify an increased risk of chronic renal impairment associated with NSAID consumption (Yaxley & Litfin 2016). Based on this study, NSAIDs do not appear to be implicated in the pathogenesis of analgesic nephropathy (*i.e.* chronic renal impairment as a direct consequence of long-term NSAID ingestion) in humans. Indeed, NSAID-associated renal toxicity of clinical significance is generally dose-related and occurs in less than 1% of the population (Curiel & Katz 2013).

RECOMMENDATIONS FOR LONG-TERM THERAPY WITH NSAIDS IN CATS WITH CKD

It is important to highlight that not all cats with CKD are good candidates for long-term NSAID administration. The International Society of Feline Medicine has published extensive guidelines on the diagnosis and management of feline CKD (Sparkes *et al.* 2016) and, based on that document and the current scientific evidence on the subject, the WSAVA-GPC recommends the administration of NSAIDs in cats with stable CKD provided that the following conditions are carefully considered:

- Stable CKD. For example, a stable patient with minimal changes in bodyweight and creatinine over a period of at least 2 months and controlled concurrent conditions including hypertension.
- The safety of NSAID therapy in cats with advanced CKD remains unknown. Most available studies have reported long-term NSAID therapy in IRIS stages 1 and 2 cats. Cats of IRIS stage 3 have also been treated but less commonly.
- Long-term maintenance of hydration. Free access to fresh water should be provided at various locations around the house. Wet food also helps to increase water intake.
- Use of the lowest or minimal effective dosage based on response to therapy. The dose can be titrated downwards or upwards by the owner according to his or her observations of the cat's behaviour in the home environment. For OA, response to therapy includes increased level of activity and ability to perform activities (*e.g.* jumping, grooming, using the litter box), improved demeanour and socialisation.

Table 1. Summary of studies evaluating the renal effects after long-term administration of non-steroidal anti-inflammatory drugs (NSAIDs) in cats with chronic kidney disease (CKD)

Study type	NSAID	Population included	Treatment protocol	Main findings	References
Retrospective case–control	Meloxicam	All cats: older than 7 years old and with evidence of OA. CKD cats of IRIS stages 1, 2 and 3. • Group A: CKD (n=22) • Group B: no CKD (n=16) • Group C: CKD (n=22) • Group D: no CKD (n=16)	Groups A and B: meloxicam (0.015 to 0.033 mg/kg PO) once daily for >6 months Groups C and D: no treatment (age- and renal status-matched controls)	• No detectable deleterious effect on renal function in groups A and B • Serum creatinine concentrations increased more slowly over time in cats in group A than group C and were not different between groups B and D • No significant differences in urine concentration ability between groups	Gowan *et al*. 2011
Retrospective	Meloxicam	All cats: older than 7 years old and with evidence of OA. CKD cats of IRIS stages 1, 2 and 3. • Group A: CKD (n=47) • Group B: no CKD (n=35)	Groups A and B: meloxicam (0.01 to 0.05 mg/kg PO) once daily for >6 months	• Cats with CKD had shorter survival than cats without CKD. However, survival after diagnosis of CKD in group A was longer than previous studies • Treatment did not appear to reduce the lifespan of cats with CKD • Most common cause of death was neoplasia for both groups	Gowan *et al*. 2012
Prospective randomised placebo-controlled	Robenacoxib	All cats: median age of 15 years old (range 6 to 20) with evidence of OA. CKD cats of IRIS stages 2 and 3. • Group A: CKD (n=18) • Group B: CKD (n=22)	Group A: robenacoxib (1 to 2 mg/kg PO) once daily for 28 days Group B: placebo (lactose) once daily for 28 days	• Bodyweight was not different from baseline or between groups • Serum creatinine or urea nitrogen concentrations were not different from baseline or between groups • Incidence of adverse effects was similar in both groups	King *et al*. 2016

OA Osteoarthritis, IRIS International Renal Interest Society

- General guidelines for the management of CKD including phosphate control should be followed.
- The risks and benefits of therapy should be thoroughly discussed with the owners with the goal of improving quality of life.
- Owner education and involvement is paramount. Owners are part of the health care team as they will be administering treatments and monitoring clinical benefits and adverse effects. The latter includes weight loss, decreased appetite, vomiting, polyuria and polydipsia.
- Ongoing monitoring should be performed via routine health checks, including changes in bodyweight, body condition scores and blood pressure, and clinical pathology tests such as haematology, serum biochemistry profile and urinalysis. There is no gold standard of when and how often these should be performed.
- Environmental enrichment techniques should always be applied in the management of chronic pain in cats. Additional, non-pharmacological techniques including physical therapy, acupuncture, nutraceuticals and chondroprotective agents might also be used, even considering that the level of evidence for these techniques is low.

LIMITATIONS OF CURRENT STUDIES

The current literature on long-term use of NSAIDs in cats with CKD has some limitations. The two studies of meloxicam in cats with CKD and OA were retrospective, and this type of study design has intrinsic limitations and is subject to numerous biases. Importantly, the author of those retrospective studies decided which cats to medicate with meloxicam, only medicating cats that were more healthy looking and in better body condition. On the other hand, these studies helped to address research questions that were poorly investigated and to identify potential risk factors, particularly when designed as a case–control study. It should also be noted that the mean dose administered in the studies with meloxicam (Gowan *et al*. 2011, 2012) was generally lower than the doses reported to be efficacious in cats (Lascelles *et al*. 2007, Gunew *et al*. 2008, Guillot *et al*. 2013). Thus, using a cautious interpretation of these studies, one might conclude that an average daily dose of 0.02 mg/kg meloxicam can be safely administered for long periods of time provided the cat looks relatively healthy (*i.e*. stable CKD). It would certainly be beneficial to have prospective randomised clinical trials using meloxicam in cats with concomitant CKD and OA. Such results would help corroborate previous findings and provide more evidence on therapeutic efficacy. With regard to the study using robenacoxib, it might be argued that the duration of treatment of 1 month was relatively short because many cats with OA may require life-long administration of NSAIDs. Nevertheless, the prospective nature of the study as a randomised, placebo-controlled design using label-recommended doses and a large population of cats represents an advantage in terms of scientific evidence and quality. We await publication of the efficacy studies.

In conclusion, based on current evidence, the WSAVA-GPC supports the long-term administration of the lowest effective doses of meloxicam and robenacoxib in cats with concomitant

chronic pain and CKD as part of a multimodal approach that includes non-pharmacological therapies, unless contraindicated. Other NSAIDs should not be used in this population of cats unless safety data for that purpose become available. Label recommendations for long-term NSAID administration might vary in different countries. The decision to treat these cats must be based on a thorough discussion with the owners as not all cats are satisfactory candidates for long-term NSAID therapy. Cats must have stable CKD, and maintenance of proper hydration is paramount. Adjuvant analgesics and non-pharmacological therapies should also be considered in cats with OA or any other chronic painful condition.

Conflict of interest

No conflict of interest has been declared.

References

Cheng, H. & Harris, R. (2005) Renal effects of non-steroidal anti-inflammatory drugs and selective cyclooxyge- nase-2 inhibitors. *Current Pharmaceutical Design* **11**, 1795-1804

Curiel, R. V. & Katz, J. D. (2013) Mitigating the cardiovascular and renal effects of NSAIDs. *Pain Medicine* **14**, 23-28

Geddes, R. F., Elliott, J. & Syme, H. M. (2013) The effect of feeding a renal diet on plasma fibroblast growth factor 23 concentrations in cats with stable azotemic chronic kidney disease. *Journal of Veterinary Internal Medicine* **27**, 1354-1361

Gowan, R. A., Lingard, A. E., Johnston, L., *et al*. (2011) Retrospective case-control study of the effects of long-term dosing with meloxicam on renal function in aged cats with degenerative joint disease. *Journal of Feline Medicine and Surgery* **13**, 752-761

Gowan, R. A., Baral, R. M., Lingard, A. E., *et al*. (2012) A retrospective analysis of the effects of meloxicam on the longevity of aged cats with and without overt chronic kidney disease. *Journal of Feline Medicine and Surgery* **14**, 876-881

Guillot, M., Moreau, M., Heit, M., *et al*. (2013) Characterization of osteoarthritis in cats and meloxicam efficacy using objective chronic pain evaluation tools. *Veterinary Journal* **196**, 360-367

Gunew, M. N., Menrath, V. H. & Marshall, R. D. (2008) Long-term safety, efficacy and palatability of oral meloxicam at 0.01-0.03 mg/kg for treatment of osteoarthritic pain in cats. *Journal of Feline Medicine and Surgery* **10**, 235-241

Hardie, E. M., Roe, S. C. & Martin, F. R. (2002) Radiographic evidence of degenerative joint disease in geriatric cats: 100 cases (1994-1997). *Journal of the American Veterinary Medical Association* **220**, 628-632

King, J. N., King, S., Budsberg, S. C., *et al*. (2016) Clinical safety of robenacoxib in feline osteoarthritis: results of a randomized, blinded, placebo-controlled clinical trial. *Journal of Feline Medicine and Surgery* **18**, 632-642

Lascelles, B. D. X., McFarland, J. M. & Swann, H. (2005) Guidelines for safe and effective use of NSAIDs in dogs. *Veterinary Therapeutics* **6**, 237-251

Lascelles, B. D. X., Hansen, B. D., Roe, S., *et al*. (2007) Evaluation of client-specific outcome measures and activity monitoring to measure pain relief in cats with osteoarthritis. *Journal of Veterinary Internal Medicine* **21**, 410-416

Lascelles, B. D. X., Henry, J. B., Brown, J., *et al*. (2010) Cross-sectional study of the prevalence of radiographic degenerative joint disease in domesticated cats. *Veterinary Surgery* **39**, 535-544

Marino, C. L., Lascelles, B. D. X., Vaden, S. L., *et al*. (2014) Prevalence and classification of chronic kidney disease in cats randomly selected from four age groups and in cats recruited for degenerative joint disease studies. *Journal of Feline Medicine and Surgery* **16**, 465-472

Mathews, K., Kronen, P., Lascelles, D., *et al*. (2014) Guidelines for recognition, assessment and treatment of pain: WSAVA global pain council. *Journal of Small Animal Practice* **55**, E10-E68

Monteiro-Steagall, B. P., Steagall, P. V. M. & Lascelles, B. D. X. (2013) Systematic review of nonsteroidal anti-inflammatory drug-induced adverse effects in dogs. *Journal of Veterinary Internal Medicine* **27**, 1011-1019

Rios, A., Vargas-Robles, H., Gámez-Méndez, A. M., *et al*. (2012) Cyclooxygenase-2 and kidney failure. *Prostaglandins and Other Lipid Mediators* **98**, 86-90

Slingerland, L. I., Hazewinkel, H. A. W., Meij, B. P., *et al*. (2011) Cross-sectional study of the prevalence and clinical features of osteoarthritis in 100 cats. *Veterinary Journal* **187**, 304-309

Sparkes, A. H., Caney, S., Chalhoub, S., *et al*. (2016) ISFM consensus guidelines on the diagnosis and management of feline chronic kidney disease. *Journal of Feline Medicine and Surgery* **18**, 219-239

Surdyk, K. K., Brown, C. A. & Brown, S. A. (2013) Evaluation of glomerular filtration rate in cats with reduced renal mass and administered meloxicam and acetylsalicylic acid. *American Journal of Veterinary Research* **74**, 648-651

Yaxley, J. & Litfin, T. (2016) Non-steroidal anti-inflammatories and the development of analgesic nephropathy: a systematic review. *Renal Failure* **38**, 1328-1334