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Acute kidney injury in 18 cats after subcutaneous meloxicam and an update on non-steroidal anti-inflammatory drug usage in feline patients in Australia

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Objectives Acute kidney injury (AKI) is a well-known but poorly documented adverse effect of non-steroidal anti-inflammatory drugs (NSAIDs) in cats. We aimed to describe instances of NSAID-associated AKI in cats and survey Australian veterinarians on NSAID use in acute settings.

Methods Medical records of cats that developed an AKI subsequent to the administration of meloxicam were obtained by searching the databases of seven practices in Queensland, as well as by contemporaneously contacting select veterinary colleagues of the authors in both general and specialist small animal practice. An online questionnaire was created for the survey, and the URL distributed to Australian practitioners.

Results A total of 18 cases were retrieved, all of which received injectable meloxicam. The indication(s) for its use and the dosage prescribed were within the manufacturer's recommendations for Australian veterinarians. The majority of cases (13/18 cats) received the label dose of 0.3 mg/kg subcutaneously (SC) on the day of the procedure. In 12/18 cats, the injection was given in association with general anaesthesia or sedation. Fourteen cats survived to hospital discharge. Of 187 survey respondees, 89% routinely administered NSAIDs for surgery-related analgesia, with 98% prescribing meloxicam and 84% of these giving it SC. Ninety percent of respondees routinely administered NSAIDs for non-surgical-related analgesia, with 99% prescribing meloxicam and 35% of those giving it SC.

Conclusions and Relevance We strongly recommend that practitioners avoid prescribing meloxicam SC in cats. This recommendation is emphatic in situations where concurrent dehydration and/or hypotension are possible.

Keywords acute kidney injury; Australia; meloxicam; NSAIDs

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Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in feline medicine to treat acute and chronic pain, fever and inflammation.[1,2] They act through the inhibition of cyclo-oxygenase (COX) enzymes, preventing the production of prostaglandins and leukotrienes involved in the inflammatory response.[3] COX inhibition also prevents the production of homeostatic prostaglandins, such as those responsible for normal platelet function, maintenance of adequate renal perfusion and cytoprotective effects at the gastric mucosa.[1] COX-2 is predominantly involved in the inflammatory response and is upregulated (i.e. inducible) at sites of inflammation, whereas COX-1 is expressed in most tissues and is mainly involved in homeostatic mechanisms (i.e. constitutive).[4]

Initially, it was thought COX-1 inhibition was responsible for most of the adverse effects reported with NSAIDs, such as gastric ulceration and kidney injury.[5] Evolving experience in human and veterinary patients has shown, however, that the COX1/COX2 paradigm is an oversimplification because COX-2 has some constitutive and COX-1 has some inducible expression.[4] Thus, adverse effects can still occur with newer generation NSAIDs, including the coxibs, which have a negligible effect on COX-1.[6,7]

In cats, the risk of adverse effects is considered low with prudent prescribing guidelines, including withholding therapy during states of hypovolaemia, hypotension and anorexia and avoiding concurrent administration of other potential nephrotoxins (the so-called 'double whammy'), such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) and diuretics (including spironolactone).[1] Due to the potential for reduced renal perfusion during anaesthesia, perioperative NSAID administration has traditionally been discouraged,[8] although recent anaesthesia guidelines reject this absolute contraindication and advocate the use of NSAIDs both prior to anaesthesia (for pre-emptive analgesia) or during recovery, as part of a balanced multi-modal analgesic plan.[9–12]

The evidence base for this altered recommendation is questionable given that NSAID-associated renal injury in cats appears to be commonly observed around the world. In Australia, meloxicam was associated with around 4% of the serious adverse animal health reports documented by the Australian Pesticides and Veterinary Medicines Authority (APVMA) for the year 2019–2020.[13] In Europe, over 900 reports of suspected meloxicam-induced renal insufficiency in cats were reported to the European Medicines Agency between

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1 January 2005 and 9 January 2022.[14] In the UK, pharmacovigilance data predicts that for every 1 million administrations of injectable meloxicam to dogs and cats, 870 will develop renal insufficiency and 684 will die.[15] Anecdotally, meloxicam is the most commonly implicated cause of adverse drug reaction seen across a large network of veterinary hospitals in the USA (Dennis Chew, personal communication January 2022).

Meloxicam (Metacam, Boehringer Ingelheim [BI]) and robenacoxib (Onsior, Elanco) are, from the experience of the authors, the two most popular NSAIDs registered for use in cats in Australia. They are COX-2 preferential and COX-2 selective, respectively.[1] Meloxicam is the most established, having been registered with the APVMA since 2007 (Metacam, BI) with the availability also of many less expensive generic meloxicam formulations subsequently. The oral suspension has a label claim in Australia for alleviation of inflammation and pain in both acute and chronic musculoskeletal disorders, using a loading dose of 0.1 mg/kg on the first day, continued once daily at 0.05 mg/kg.[16] The injectable formulation has a label claim in Australia for reduction of pain after surgery using a single dose of 0.3 mg/kg subcutaneously (SC) immediately prior to induction of anaesthesia.[17] These dosages are widely used and accepted,[1] although some recent guidelines recommend a lower 0.2 mg/kg SCI (subcutaneous injection) dose.[12] Labels on both oral and parenteral formulations warn against use in dehydrated, hypovolaemic or hypotensive animals due to the potential risk of causing acute kidney injury (AKI), although the manufacturers do not list a requirement or even recommend testing renal analytes in serum or determining urine specific gravity (USG) prior to administration of meloxicam for acute pain.[16,17] Such a requirement would seem prudent, given the well-understood ability of cats to hide clinical signs of disease including dehydration.

Despite the stated warnings, it remains unclear (i) when, (ii) how often and (iii) why AKI occurs in cats. Furthermore, the frequency of this occurrence and the prognosis for affected cats, once AKI has occurred, is not well documented. Thus, there has been a complete failure of post-marketing surveillance to establish whether the practice of administering NSAIDs in various settings is indeed safe when administered to a large cohort of cats.

Robson and New Zealand colleagues, in a 2006 ACVIM scientific abstract, describe 16 kittens (age range 3–8 months; mean 5.7 months) that developed an AKI following routine desexing, having received injectable carprofen, meloxicam or ketoprofen in the perioperative period.[18] Four cats were euthanised when severe azotaemia did not resolve with therapy, four cats survived with azotaemic chronic kidney disease (CKD) and eight cats recovered with complete resolution of azotaemia. A French study described 21 cats diagnosed with AKI 2–15 days following a SCI or intramuscular (IM) injection of nimesulide, tolfenamic acid or ketoprofen.[19] Details of the cats at the time of NSAID administration and the indication for NSAID use were not specified and the mortality rate was 25%, mostly associated with papillary necrosis. Supportive therapy for up to 4 weeks was required in some survivors.

The aim of this study was to describe NSAID-associated AKI in Australian cats as a clinical entity, and document the clinical histories of 18 cats that developed an AKI following a SCI of meloxicam. To better understand how and why this might happen, our secondary aim was to survey the prescribing habits of Australian practising clinicians regarding their use of NSAIDs in cats, as available data on this subject is now over 25 years old.[20] Following data analysis, we discuss recommendations to make the use of NSAIDs in cats safer, thereby hopefully reducing the incidence of AKI in feline patients.

Methods

Case series

Clinical records from January 2007 to January 2021 containing the words 'acute kidney injury', 'AKI', 'acute renal failure' or 'ARF' and 'Metacam' or 'meloxicam' were retrieved from the practice databases of Veterinary Specialist Services (VSS) Underwood, Jindalee and Carrara, QLD (ezyVet; ezyVet, New Zealand), Animal Emergency Service (AES) Underwood, Jindalee and Carrara, QLD (RxWorks; Covetrus, Australia) and Animal Referral Hospital (ARH), Sinnamon Park, QLD (RxWorks; Covetrus, Australia). VSS and AES operate within the same premises, managing day-time and after-hours cases, respectively. Additional cases and their medical records were obtained contemporaneously by contacting colleagues of the authors. In cases where meloxicam was administered in primary care veterinary hospitals, medical records were obtained from that facility. All cases with a diagnosis of NSAID-associated AKI were enrolled, and relevant data from their records were extracted. A definitive diagnosis was made based on a combination of IRIS AKI Grade 3[21] or higher with a USG <1.040, and the development of clinical signs consistent with AKI (lethargy, anorexia or vomiting) within 9 days of NSAID administration. In cases where USG was unavailable, a presumptive diagnosis was made based on IRIS AKI Grade 3 or higher persisting despite 24 hours of intravenous fluid therapy. Cats with known systemic co-morbidities prior to NSAID administration (e.g. azotaemia [serum urea and/or creatinine concentrations above the reference interval (RI) provided by the laboratory or manufacturer of the in-clinic instrument], abdominal or thoracic trauma, dehydration, or other clinical signs of systemic disease) and cases where the dose or route of NSAID administered was unknown, were excluded.

For each case, the signalment, body weight, body condition score, reason for providing analgesia, timing, dose and route of NSAID administered, time from first NSAID dose to the onset of clinical signs, time from the first NSAID dose to the commencement of treatment, serum creatinine, urea, potassium and phosphorus concentrations and USG immediately prior to treatment, duration of hospitalisation and serum creatinine and urea at the end of the hospitalisation period, were extracted from the medical records. Serum biochemical analyses were performed using in-clinic machines (Catalyst One, IDEXX; VETSCAN VS2, Zoetis) or at a reference laboratory. USG was measured using a handheld refractometer (medical or feline specific; the latter used by the reference laboratories). Packed cell volume (PCV) was measured in-clinic using a microhematocrit centrifuge, whereas haematocrit (HCT) was measured at the reference laboratories. Where NSAID administration was associated with general anaesthesia, blood pressure was monitored using indirect oscillometry or Doppler, and details of the anaesthetic regime were recorded. When available, serum creatinine

and urea concentrations and USG prior to meloxicam administration and following discharge were reviewed to provide evidence of pre-existing and ongoing azotaemia, respectively. Abdominal ultrasound reports and urine culture results were also reviewed and cases were excluded if other potential causes of AKI were identified (e.g. urinary tract infection, ureteric obstruction, renal mass).

All cases were initially treated with intravenous fluid therapy (IVFT), generally using Hartmann's solution with rates ranging from 3–9 mL/kg/h. One case was treated with Hartmann's solution initially, then transitioned to 0.45% NaCl (w/v) and 2.5% glucose (w/v) solution containing 20 mmol KCl/L. In two cases the rate was not recorded, and in 1 case, the rate was continuously altered to match urine output (UOP). Some cases received antiemetics (metoclopramide, maropitant and/or ondansetron), gastroprotective agents (esomeprazole, omeprazole, ranitidine and/or the prostaglandin analogue misoprostol), analgesia (methadone, fentanyl, buprenorphine and/or gabapentin), amoxicillin-clavulanic acid and/or mirtazapine, at the discretion of the treating veterinarian. A urinary catheter was placed in one patient to monitor UOP; this case received intermittent furosemide boluses, a mannitol bolus and a mannitol constant rate infusion (CRI) when UOP declined. One other case also received a mannitol bolus, although UOP was not recorded. No cases received peritoneal dialysis or renal replacement therapy. One case received insulin and a glucose bolus to treat hyperkalaemia.

Survey

An online questionnaire (Appendix S1) was created using SurveyMonkey (Momentive Inc., San Mateo), and the URL distributed via email to members of the Australian and New Zealand College of Veterinary Scientists (ANZCVS) and to referring veterinary clinics in the practice databases of VSS and Sydney Veterinary Emergency & Specialists (SVES), Rosebery, NSW. The survey URL was also published in the fortnightly online newsletter sent to members of the Australian Veterinary Association, on the public Facebook (Meta, Menlo Park) page of The Sydney School of Veterinary Science, The University of Sydney and the online forum of the International Society of Feline Medicine (ISFM) Academy of Feline Practitioners. Survey responses were collected between 1 October 2020 and 31 December 2021. Only responses from veterinarians currently practising in Australia were included in the analysis.

The questionnaire first asked when the participant graduated as a veterinarian and in which state/territory they currently practised. In relation to young adult cats with normal hepatic, cardiac and renal function, they were then asked whether and what NSAID they routinely administer for surgery-related analgesia (e.g. associated with dental extractions, desexing, or any other surgery), as well as timing, route and dose prescribed. They were then asked the same questions in relation to non-surgery-related analgesia (e.g. musculoskeletal disorders, idiopathic cystitis). Finally, respondents were asked whether they had diagnosed AKI in a cat that had received an NSAID in the 2 weeks prior to the development of AKI.

Statistical analysis

Descriptive statistics (medians, total range and interquartile ranges) were performed using Microsoft Excel (Microsoft Excel for Mac Version 16.66.1, Microsoft Corporation, Redmond, Washington).

Results

Retrospective case series of AKI in cats

Eighteen cases meeting our inclusion criteria were found. Fourteen were retrieved from the practice databases of VSS (5 cases), AES (7 cases) and ARH (2 cases), while the remaining four were obtained from colleagues. All cases involved meloxicam. It was administered at a primary care veterinary hospital in 17 cases; in the remaining case, meloxicam was administered at VSS. Salient clinical data are summarised in Table 1. Of these cases, 15 were diagnosed definitively, and three cases were diagnosed presumptively. Cases comprised 11 Domestic Short-haired cats, two Siamese and one each of Domestic Medium-hair, British Short-hair, Russian Blue, Turkish Angora and a mixed breed. Median age and body weight was 6 years (range 5 months–15 years, IQR 2.25–9 years) and 5.0 kg (range 2.3–7.6 kg, IQR 4.2–5.7 kg), respectively. The median body condition score was 5/9 (range 4–8, IQR 4.0–5.5). In eight cases, serum creatinine and urea concentrations measured prior to meloxicam administration were unretrievable but reported to be within the RI provided by the laboratory or manufacturer of the in-clinic instrument. The pre-meloxicam serum creatinine value was retrievable in four cases (median 135.5 μmol/L, range 62–150 μmol/L, IQR 113–143.3 μmol/L); the serum urea concentration was retrievable in three cases (median 6.7 mmol/L, range 4.7–17 mmol/L, IQR 5.7–11.2 mmol/L). In addition, 2 cases were documented to be non-azotaemic 2 and 8 months prior to meloxicam administration; cases 4 (serum creatinine 46 μmol/L, urea 4.2 mmol/L) and 12, respectively.

The reasons for prescribing meloxicam were: tooth extraction(s) (7 cases), lameness (2 cases), skin wounds (2 cases) and one case each of castration, conjunctivitis, corneal ulcer, otitis externa, constipation, arthritis and a cutaneous mass biopsy (focal perianal vasculitis). Meloxicam was given by SCI in all cases, at a median dose of 0.3 mg/kg (range 0.1–0.3 mg/kg, IQR 0.23–0.30 mg/kg).

After AKI developed, six cases had an abdominal ultrasound (with a specific focus on the kidneys) performed by a registered specialist in internal medicine, with no abnormalities reported. Five cases had negative urine bacterial culture results on testing.

In 11/18 cats, the meloxicam injection was given in association with general anaesthesia. It was given during general anaesthesia in three cats, during recovery (intubated but off isoflurane) in one cat and after recovery (extubated and conscious) in five cats. In two cats, the timing of administration was unrecorded, but meloxicam was given by SCI on the day of the anaesthetic. Cats were premedicated with acepromazine (8 cats; 0.02–0.1 mg/kg) or medetomidine (2 cats; 4–10 μg/kg) in conjunction with methadone (8 cats; 0.2–0.4 mg/kg) or butorphanol (1 cat; 0.2 mg/kg), administered SC or IM. Cats were induced with either alfaxalone (10 cats) or thiopentone (1 cat) and maintained using isoflurane in 100% oxygen. One cat received the meloxicam SCI after medetomidine/butorphanol sedation. Nine of these 12 cats received Hartmann's IVFT during anaesthesia/sedation,

TABLE 1. Summary of meloxicam-associated acute kidney injury cases in cats

CASE	Date	Signalment	Urea (mmol/L) and Cr (μmol/L) on day of meloxicam dose	Indication for meloxicam	General anaesthesia or sedation	IVFT during anaesthesia or sedation	Initial meloxicam dose, route; timing	Additional meloxicam doses	Initial and final Cr (μmol/L)	Time in hospital (days)	Outcome
1	18 July 2015	15 years FS Siamese	8.1, 181	Tooth extraction	General anaesthesia	5 mL/kg/h	0.3 mg/kg SCI; during anaesthesia	None	1202, 1108	1	Euthanised
2	25 June 2016	15 years FS British Short-hair	Unknown	Arthritis	No	n/a	0.15 mg/kg SCI	0.05 mg/kg PO for 7 days	1202, 1064	1	Euthanised
3	28 May 2018	12 years FS DSH	Within RR	Lameness	No	n/a	0.2 mg/kg SCI	0.2 mg/kg SCI 2 days later	480, 1202	1	Euthanised
4	3 April 2022	5 months MN DSH	Unknown	Castration	General anaesthesia	3 mL/kg/h	0.3 mg/kg SCI; after recovery	None	1044, unknown	0.5	Euthanised
5	29 March 2011	3 years MN Siamese	Unknown	Skin wounds	General anaesthesia	Unknown	0.3 mg/kg SCI; unknown	None	1140, 550	3	Discharged. 2 weeks later Cr 775 μmol/L, USG 1.010. Euthanised
6	6 September 2013	6 years FS DSH	Unknown	Conjunctivitis	No	n/a	0.3 mg/kg SCI	0.05 mg/kg PO for 6 days	1490, 313	6	Discharged. 1 day later Cr 731 μmol/L. IVFT recommenced for 6 days, final Cr 163 μmol/L. Non-proteinuric stage 2 CKD 4 weeks later. Stage 4 CKD 5 years later, euthanised.
7	18 June 2014	2 years FS DSH	Unknown	Lumpectomy	General anaesthesia	Unknown	0.3 mg/kg SCI; during recovery	0.3 mg/kg SCI 3 days later	520, 128	4	Discharged. Alive 5 years later
8	29 July 2014	2 years MN Russian Blue	Unknown	Tooth extraction	General anaesthesia	8 mL/kg/h	0.3 mg/kg SCI; during anaesthesia	0.05 mg/kg PO for 3 days	1155, 180	3	Discharged. Alive 4 years later
9	16 January 2016	1 year MN DSH	Unknown	Lameness	No	n/a	0.3 mg/kg SCI	0.05 mg/kg PO 3 days later	1166, 149	3	Discharged and lost to follow-up
10	24 April 2016	9 years MN DSH	Within RR	Tooth extraction	General anaesthesia	10 mL/kg/h	0.3 mg/kg SCI; after recovery	None	397, 156	2	Discharged. Stage 2 CKD 2 months later. Alive 4 years later
11	14 May 2016	4 years FS DSH	Unknown	Otitis externa	No	n/a	0.2 mg/kg SCI	None	440, 100	2	Discharged and lost to follow-up
12	26 May 2016	10 years MN DSH	Unknown	Corneal ulcer	No	n/a	0.2 mg/kg SCI	0.2 mg/kg SCI 3 days later	776, 291	3	Discharged and lost to follow-up
13	14 November 2016	2 years MN Turkish Angora	Within RR	Skin wounds	General anaesthesia	10 mL/kg/h	0.3 mg/kg SCI; after recovery	None	676, 141	4	Discharged. Non-azotaemic 8 days later
14	6 January 2019	9 years FS mixed breed	17, 150	Tooth extraction	General anaesthesia	Unknown	0.3 mg/kg SCI; unknown	0.3 mg/kg SCI 3 days later	2810, 630	14	Discharged. 250 mL SQ fluids given twice a week. Non-proteinuric stage 3, CKD 1 month later, which was static 3 months later.
15	4 February 2020	9 years FS DSH	47, 62	Constipation	Sedation	3 mL/kg/h	0.3 mg/kg SCI; during sedation	None	1326, 486	2	Discharged. 3 days later Cr 601 μmol/L. Lost to follow-up
16	22 May 2020	5 years MN DSH	Unknown, 130	Tooth extraction	General anaesthesia	5 mL/kg/h	0.1 mg/kg SCI; after recovery	None	555, 98	9	Discharged. 3 weeks later Cr 159 μmol/L. 3 months later Cr 199 μmol/L. Alive as of January 2021
17	8 June 2020	6 years MN DSH	6.7, 141	Tooth extraction	General anaesthesia	3 mL/kg/h	0.3 mg/kg SCI; during anaesthesia	None	510, 335	2	Discharged. 4 days later Cr 320. Daily SQ fluids started. Alive as of January 2021

18	16 December 2020	8 years MN DLH	Unknown	Tooth extraction	General anaesthesia	3 mL/kg/h	0.3 mg/kg SCI; after recovery	0.05 mg/kg PO for 3 days	956, 215	5	Discharged. 1 day later Cr 264 µmol/L. 2 days later Cr 349 µmol/L. IVFT recommenced for 2 days, after which Cr 211 µmol/L. Discharged with SQ fluids. 1 month later Cr 159 µmol/L. Lost to follow-up

Abbreviations: Cr, serum creatinine; FS, female spayed; IVFT, intravenous fluid therapy; MN, male neutered; PO, by mouth; RR, laboratory reference range; SCI, subcutaneous injection; SQ, subcutaneous; Timing, the timing of administrating when meloxicam was administered in association with general anaesthesia or sedation; USG, urine specific gravity.

at rates ranging from 3 to 10 mL/kg/h for the duration of the procedure. Sustained hypotension was not documented in any case.

Nine of the 18 cats received additional meloxicam following the first injection. In five cats, this was given orally at a dose of 0.05 mg/kg per day; this was started the day following the procedure in four cats and given for 3–5 consecutive days, whilst the remaining cat received a single dose 3 days after the initial injection. Four cats received one additional SCI of meloxicam (ranging from 0.2–0.3 mg/kg) given 2–7 days after the initial injection. The median time from the first meloxicam dose to (i) onset of clinical signs and (ii) commencement of treatment was 4 days (range 1–11 days, IQR 2.3–4 days) and 5.5 days (range 3–12 days, IQR 4–8.8 days), respectively. The most common clinical sign was lethargy (18/18; 100%), followed by decreased appetite (15/18; 83.3%), vomiting (9/18; 50.0%) and polyuria/polydipsia (2/18; 11.1%).

Immediately prior to commencing treatment for AKI using IVFT, median analyte concentrations were as follows: serum creatinine concentration 1,000 µmol/L (range 397–2,810 µmol/L, IQR 528.8–1,202 µmol/L; $n = 18$), urea 43.3 mmol/L (range 20.8–106.4 mmol/L, IQR 39.6–49.1 mmol/L; $n = 18$), potassium 5.3 mmol/L (range 3.1–9.0 mmol/L, IQR 4.9–6.8 mmol/L; $n = 13$), inorganic phosphorus 3.8 mmol/L (range 0.78–8.82 mmol/L, IQR 3.07–5.06 mmol/L; $n = 13$), PCV/HCT 0.38 L/L (range 0.26–0.52 L/L, IQR 0.36–0.45 L/L; $n = 15$) and total plasma protein concentration 77 g/L (range 64–92 g/L, IQR 72.5–89.8 g/L; $n = 13$) (Table 1). The median duration of hospitalisation was 3 days (range 0.5–14 days, IQR 2.0–4.8 days). Median serum creatinine and urea concentrations at the end of the hospitalisation period in cats that survived were 197.5 µmol/L (range 98–630 µmol/L, IQR 149–550 µmol/L; $n = 14$) and 9.4 mmol/L (range 4.4–30.7 mmol/L, IQR 7.5–16.6 mmol/L; $n = 14$), respectively. One cat (case 16) had a period of oliguria (UOP 0.8 mL/kg/h) that resolved after IV furosemide (0.5 mg/kg), while another cat (case 4) remained anuric throughout the 12-hour hospitalisation period. Oliguria or anuria were not documented in other cases, although UOP was not specifically measured.

Fourteen of the 18 cats (77.8%) survived to hospital discharge. Follow-up information was available for 11 and is summarised in Table 1. The remaining cats were euthanised due to a marginally decreased or increased serum creatinine concentration after 24 hours of IVFT (3 cats) or the development of anuria (1 cat).

Survey

A total of 203 veterinarians responded to the survey. Sixteen responses from clinicians practising outside Australia were excluded. Thus, 187 responses were included in the analyses (58 from NSW, 30 from Victoria, 81 from Queensland, 10 from WA, 3 from SA and 8 from the ACT). Respondents were a mix of recent graduates and more experienced practitioners, with 24 (13%) having had their veterinary degree for <5 years, 34 (18%) for 5–10 years, 60 (32%) for 10–20 years, 50 (27%) for 20–30 years and 35 (19%) for >30 years.

In relation to young adult cats with normal hepatic, cardiac and kidney function, 166/187 (89%) of respondees routinely administered NSAIDs for surgery-related analgesia, with the vast majority (162/187 [98%]) prescribing meloxicam. Robenacoxib was used by only 3/187 (2%) clinicians. Of meloxicam prescribers, 136/162 (84%) administered it SC, at doses of 0.3 mg/kg (49/136 [36%]), 0.2 mg/kg (43/136 [32%]), 0.15 mg/kg (1/136 [1%]), 0.1 mg/kg (39/136 [29%]) and 0.05 mg/kg (4/136 [3%]). If ongoing analgesia was required, most practitioners (128/136 [94%]) followed up this injection with the oral formulation, commencing on the same day (4/128 [3%]), the next day (89/128 [70%]) or 2–3 days later (34/128 [27%]), whilst one respondent gave an additional SCI 3 days after the first. The remaining seven veterinarians (5%) did not prescribe additional meloxicam following the injection. Twenty-six of 162 (16%) respondents prescribed oral meloxicam only. An oral dose of 0.05 mg/kg once a day was most often prescribed (128/149 [86%]), followed by 0.1 mg/kg initially then 0.05 mg/kg on each subsequent day (18/149 [12%]) and <0.05 mg/kg once a day (3/149 [2%]).

Meloxicam prescribers administered the drug during the recovery period (80/160 [50%]), after recovery (67/160 [42%]), during anaesthesia (11/160 [6.9%]) and the day following surgery (2/160 [1.3%]).

In relation to young adult cats with normal hepatic, cardiac and renal function, 169/187 (90%) of respondees routinely administered NSAIDs for non-surgery-related analgesia, with the great majority again prescribing meloxicam (166/168 [99%]), as opposed to robenacoxib (2/168 [1%]). Of meloxicam prescribers, only 58/166 (35%) administered it SC, at doses of 0.3 mg/kg (23/58 [40%]), 0.2 mg/kg (13/58, [22%]), 0.1 mg/kg (19/58 [33%]) and 0.05 mg/kg (2/58 [3%]). If ongoing analgesia was required, most practitioners (55/58 [95%]) followed up this injection with the oral formulation, commencing on the same day (2/55 [4%]), the next day (39/55 [70%]) or 2–3 days later (14/55 [26%]). The remaining three practitioners (5%) did not prescribe additional meloxicam following the injection. A total of 108/166 (65%) respondents prescribed oral meloxicam only for non-surgery-related analgesia. An oral dose of 0.05 mg/kg once a day was most often prescribed (127/164 [77%]),

followed by 0.1 mg/kg initially then 0.05 mg/kg on each subsequent day (33/164 [20%]) and <0.05 mg/kg once a day (3/164 [2%]).

Finally, 70/187 (37.4%) of respondents reported having diagnosed AKI in a feline patient that had received an NSAID in the 2 weeks preceding this presentation, all of which received meloxicam.

Discussion

Despite AKI being a well-known adverse effect of NSAIDs, meloxicam remains an important drug in feline medicine for both its anti-inflammatory and analgesic properties and especially for the long-term management of osteoarthritis (OA). When given orally and at constant low doses (0.01–0.03 mg/kg SID), it is an inexpensive and generally safe medication, even in cats with pre-existing CKD, although it should still be used with caution due to the potential for increased proteinuria.[22–24] For it to be given safely, it is important to avoid its use in specific situations, including dehydrated, hypovolaemic or hypotensive patients and in cats in which pre-existing AKI is likely or possible, such as cats that have had a urethral or ureteric obstruction or been administered nephrotoxic drugs (such as gentamicin, doxorubicin or amphotericin B) or potentially-nephrotoxic drugs (ACE inhibitors, ARB, diuretics including spironolactone).[1]

Meloxicam is not considered inherently nephrotoxic.[25] NSAIDs cause AKI only when systemic vasoconstrictor signals become activated following hemodynamic challenges, such as sodium depletion, volume contraction, hypotension, shock and general anaesthesia.[25] Normal renal vascular resistance and blood flow are relatively well-maintained during times of vasoconstriction, provided the synthesis of renal vasodilator substances is normal. Renal vasoconstriction, however, proceeds unopposed if the synthesis of renal vasodilatory prostaglandins is blocked by NSAIDs. In these instances, progression to azotemic AKI and papillary necrosis may occur.[25] It would therefore appear prudent to avoid NSAIDs on the day of general anaesthesia, especially in a species where the accurate measurement of blood pressure is challenging,[26] and particularly in practices and shelters where anaesthesia may be intermittently monitored by multi-tasking staff, rather than a dedicated veterinary anaesthetist. Indeed, anaesthetic monitoring in some veterinary practices can be less than ideal and the isoflurane vaporiser might be left on at 2% for the duration of short anaesthetic procedures despite a deepening plane of anaesthesia. For this reason, the potential for transient unwitnessed hypotension is far greater in feline than in human anaesthesia, or in the setting of a veterinary teaching hospital.

The 18 cases of AKI reported here were all associated with a SCI of meloxicam at doses less than or equal to the recommended dose of 0.3 mg/kg. The majority of affected cats received 0.2 to 0.3 mg/kg of meloxicam SC. As the manufacturer's recommended oral dose for this drug in cats for chronic administration is 0.05 mg/kg/day,[16] these doses are 4–6 times as high as those recommended in cats for acute and chronic musculoskeletal disorders and 10 to 30 times the maintenance doses that tend to be given long-term for osteoarthritis (0.01–0.03 mg/kg SID).[22,23] In effect, cats are given a loading dose SC to fill up meloxicam's volume of distribution, thereby rapidly achieving high therapeutic blood concentrations to provide adequate surgical analgesia.

To date, five small studies have assessed the safety of meloxicam SC on the day of anaesthesia. As part of an FDA New Animal Drug Application, meloxicam was administered SC (0.3 mg/kg) to six conscious cats aged between 7 and 36 months once a day for 3 days.[27] Azotaemia was not observed in any cat, although it is unclear when serum creatinine and urea were measured. Carroll and colleagues reported 72 cats aged four to 192 months that received meloxicam SC (0.3 mg/kg) before onychectomy under general anaesthesia; serum creatinine and urea 24 hours after surgery were not significantly higher than prior to surgery and not significantly different to 66 cats that received butorphanol in place of meloxicam.[28] In 50 cats aged over 16 weeks given meloxicam SC (0.2 mg/kg) before or after onychectomy combined with neutering under general anaesthesia, followed by 0.05 mg/kg once a day for 3–5 days, azotaemia was not identified in any cats 3 and 5 days following the procedures.[29] All cats in these studies received IVFT and blood pressure monitoring throughout general anaesthesia.[29] A similar study, published as a thesis from the Budapest veterinary school, showed safety in 9 cats aged three to 36 months subjected to neutering.[30] In a study from New Zealand, 24 cats were given carprofen (4 mg/kg), meloxicam (0.2 mg/kg) or saline (as a control) via SCI with their premedication prior to dental procedures done under anaesthesia; plasma iohexol clearance and urinary N-acetyl-β-D glucosaminidase activity were unaffected by the NSAID administration in treated compared to control cats.[31]

Although these five studies concluded that administration of meloxicam via SCI is safe, the study population of cats is likely much younger than the general cat population, as onychectomy and neutering are generally performed before adulthood. As kittens are unlikely to have age-related degeneration of the kidney, they may be less susceptible to AKI given that renal azotaemia requires a loss of 75% of renal function to be detected.[32] Glomerular filtration rate after the procedures was only measured in one study and testing of urine for glycosuria or casts to determine if subclinical renal injury occurred was not done except in the NZ study that measured urinary N-acetyl-β-D glucosaminidase activity. Critically, these studies have not been substantiated by post-marketing surveillance under field conditions in which much larger numbers of cats were treated under less optimal circumstances and followed up. It is also possible that in the overall feline population there is a small subset of cats that for some reason are much more susceptible to the effects of meloxicam than normal cats (Nicholas Villarino, personal communication).

The time from the first meloxicam dose to the onset of clinical signs in our study cohort was highly variable, ranging from 1 to 11 days. The short-term prognosis for meloxicam-associated AKI appears to be good with appropriate and timely treatment, with 14/18 cases surviving to hospital discharge with a relatively short median duration of hospitalisation (3 days). In addition, the three cats that were euthanised after showing marginally decreased or increased serum creatinine concentrations after 24 hours of IVFT may have survived if given more time, including measures such as renal replacement therapy (e.g. peritoneal dialysis or haemodialysis), as the recovery phase of AKI can take as long as weeks-months to occur.[33]

The medium to long-term prognosis was variable within our study population and limited post-discharge information for most cases

makes drawing definitive conclusions difficult. However, cases 13, 14, 16 and 18 show that even cats presenting with IRIS Grade V AKI have the potential to recover and live for many years, although residual kidney damage resulting in CKD is common.

The 18 cases described here are reminiscent of the 16 kittens described by Robson and colleagues that developed an AKI following routine desexing in New Zealand, having received an injectable NSAID in the perioperative period.[18] After reading their ACVIM abstract, we contacted the authors of the study, and further details of the cases were obtained (Table 2; Appendix S1). While 10 cats received either an older generation, less COX-2 selective NSAID (ketoprofen or carprofen) or meloxicam at slightly above the manufactures Australian recommended dose, six cats received meloxicam SC at the label dose (0.3 mg/kg). None of the cats had pre-operative blood work, but all kittens were considered healthy by their owners and unremarkable on physical examination pre-operatively. An intravenous anaesthetic agent only (propofol, alfaxalone or thiopentone) was used in 13 cats, whilst the remaining cats were maintained subsequently with halothane or isoflurane. No cat received fluid therapy or blood pressure monitoring. These cases show that even healthy young kittens may be susceptible to NSAID-induced AKI (including meloxicam), especially when paired with anaesthesia protocols that do not support optimal renal perfusion.

Our survey results show that Australian veterinarians widely prescribe NSAIDs for both surgery and non-surgery-related analgesia in cats, with meloxicam dominating the market by a substantial margin. The SCI route of administration is widely used for providing surgical-releated analgesia, although the dose and timing of administration varied widely between respondees, ranging from the 0.3 mg/kg label dose down to 0.05 mg/kg given during anaesthesia, during recovery, after recovery or the day following surgery. The oral formulation was preferred by most practitioners for non-surgical analgesia, although a SCI was still used by over a third of responders.

Due to its retrospective nature, this case series has several limitations. First, we cannot exclude the possibility of pre-existing advanced CKD in the 10 cats in which baseline serum creatinine and urea concentrations were unavailable on the day of meloxicam administration. We consider this unlikely given the complete absence of any of the expected clinical signs (vomiting, anorexia, lethargy, polyuria/polydipsia, dehydration, shrunken kidneys). Subclinical renal insufficiency may have been present in these cats and the four cats with unrecorded creatinine and urea values, as creatinine and urea concentrations within the RI do not preclude IRIS Stage I or II CKD.[34] Secondly, AKI induced by anaesthesia or sedation-related hypotension, or poor renal perfusion, was possible in 12 cases, although the majority received adequate to generous fluid rates during anaesthesia.[9] We appreciate that in some cats fluid therapy alone will not correct hypotension, and other measures may be required such as reducing the vaporiser setting if the plane of anaesthesia is too deep. Importantly, six cases of AKI were not in any way associated with anaesthesia or sedation. Thirdly, other causes of AKI (e.g. pyelonephritis, ureteral obstruction, kidney neoplasia) are possible in the 14 cases that did not have an abdominal ultrasound and the 13 cases that did not have a urine culture performed.

Perhaps the survey's most striking finding was that roughly one-third of veterinarians responding to the survey had seen likely NSAID-induced AKI, suggesting this was a widely occurring complication in companion animal practice. We would encourage veterinarians to report suspected cases to the specific drug manufacturer or the Adverse Experience Reporting Program, which is a post-registration program assessing reports of adverse experiences associated with the use of registered chemical products run by the APVMA.[35] Only through systematic pharmacovigilance will it be possible to estimate the overall frequency of this occurrence, as has been attempted in a study from the UK.[15] Anecdotally, feline and internal medicine specialists in Australia commonly treat and provide advice about these cases on an ongoing basis, consistent with this being an important and common problem. The authors, therefore, recommend that practitioners avoid administering meloxicam SC, especially at the label dose (0.3 mg/kg). We do not know if the problem is the susceptibility of a particular group of cats, or if transient hypotension is common in feline anaesthesia in veterinary practice. For whatever reason, NSAID-induced AKI is an easily preventable cause of morbidity and mortality.

TABLE 2. Summary of NSAID-associated acute kidney injury in cats reported by Robson et al. (2006)

Number of cases	NSAID	Initial dose and route	Additional doses[a]
4	Carprofen	≤4 mg/kg IV/SQ	n/a
1	Carprofen	Unknown	Unknown PO dose once 4 days later
1	Carprofen	≤4 mg/kg IV/SQ	Unknown doses of injectable and oral meloxicam 2 days later
5	Meloxicam	≤0.3 m/kg SQ	n/a
1	Meloxicam	0.4 mg/kg SQ	n/a
1	Meloxicam	Unknown	n/a
1	Meloxicam	0.3 mg/kg SQ	0.05 mg/kg PO for 3 days
1	Meloxicam	0.5 mg/kg SQ	0.05 mg/kg PO for 1 day
1	Ketoprofen	≤ 2 mg/kg IV/SQ/IM	≤0.25 mg/kg PO once 2 days later

[a] Four cats were euthanised due to failure of severe azotaemia to resolve, four cats survived with azotemic chronic kidney disease (CKD), and eight cats recovered with complete resolution of azotaemia.

For surgical-related analgesia, balanced anaesthesia approaches incorporating the use of an opioid and possibly ketamine readily and safely provides excellent intraoperative analgesia, while long-acting opioid formulations can be given at the end of the procedure to provide analgesia until the next day when the patient has recovered sufficiently to take an oral NSAID such as meloxicam or robenacoxib once eating and drinking has resumed. This is consistent with most human analgesic guidelines, which recommend NSAID use in the post-operative period only.[36] For non-surgery-related analgesia, we recommend oral meloxicam (0.05 mg/kg orally once a day with food) without a loading dose,[22–24] or long-acting opioid formulations or transmucosal buprenorphine if the patient is not eating reliably.

Veterinarians in Australia may prefer NSAIDs to opioids and ketamine as they do not require the extra step of Schedule 8 drug registration. This would be a poor reason for avoiding the use of opioids, which provide unrivalled analgesia at therapeutic doses with a wide safety margin safety at an economical price.[37–39] For example, the cost for 3 doses of buprenorphine (which provides 24 hours of analgesia[12]) in a 5 kg cat is approximately $2.40 AUD,[1] which compares favourably to a single dose of SC meloxicam ($1.00).[2]

Routine surgical neutering, dental procedures including most extractions, idiopathic cystitis and corneal ulcers are not considered causes of major pain. Intraoperative incorporation of an opioid and possibly ketamine, combined with the use of local anaesthesia plus long-acting opioids provide safe, long-lasting multi-modal analgesia. There seems no justification to routinely use NSAIDs pre-emptively, as there is, for whatever reason, a real risk of AKI in a finite but small proportion of cases.

Conclusions

The routine use of injectable NSAIDs is not safe in contemporary feline practice for reasons that are not currently clear. There is no justification for even a small proportion of cats developing AKI when safe and inexpensive alternative analgesic regimens are available. It behoves us to remember the old dictum—*primum non nocere* (at first do no harm)—when developing drug regimens for commonly performed routine procedures in feline practice.

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[1]Based on a $23.45 market price for Ilium Temvet 0.3/mL buprenorphine 10 mL, using a dose of 0.02 mg/kg (www.provet.com.au, accessed 21/09/2022).
[2]Based on a $60.05 market price for meloxicam 5 mg/mL 20 mL, using a dose of 0.3 mg/kg (www.provet.com.au, accessed 21/09/2022).

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site: http://onlinelibrary.wiley.com/doi/10.1111/avj.13222/suppinfo.

Appendix S1. Supplementary information.

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