



Evaluation of the adverse effects of subcutaneous carprofen over six days in healthy cats

P.V.M. Steagall^{a,b,*}, F.Q. Moutinho^b, F.B. Mantovani^b, D. Passarelli^b, A. Thomassian^b

^a Department of Surgical Sciences, University of Wisconsin-Madison School of Veterinary Medicine, 2015 Linden Dr, Madison, WI 53706, USA

^b Department of Surgery and Veterinary Anesthesiology, School of Veterinary Medicine and Animal Science, São Paulo State University, Distrito de Rubião Jr., s/n, 18600-000, UNESP Botucatu-SP, Brazil

Accepted 15 April 2008

Abstract

This study evaluated the adverse effects of carprofen in seven healthy cats. Values for CBC, biochemical profiles and platelet aggregation were measured before and at seven days after SID treatment with subcutaneous carprofen: 4 mg/kg (day 1), 2 mg/kg (day 2 and 3) and 1 mg/kg (day 4 and 6) (CG) or 0.35 ml of saline (SG) for six days in a randomized, blinded, cross-over study with a four-week wash-out period. No treatment was given on day 5. Endoscopy of the GI tract was performed pre-treatment and on day 7 post-treatment. There were no significant changes in hematological profiles, biochemical profiles and endoscopy grading scores within nor between groups, except for lower albumin values at baseline than on day 7 (CG), and globulin and ALP values were higher at baseline than on day 7 in CG and SG. SC administration of carprofen over six days did not cause any adverse effects on gastrointestinal, hematological, or serum biochemical variables.

© 2008 Elsevier Ltd. All rights reserved.

Keywords: Cat; Carprofen; NSAIDs; Adverse effects; Analgesia; Pain

1. Introduction

The use of analgesics in cats has recently increased compared to 15 years ago (Dohoo and Dohoo, 1996; Hewson et al., 2006). A recent survey performed in Canada revealed no differences in the use of postoperative analgesics between dogs and cats (Hewson et al., 2006), whereas in 1996, there were significant interspecies differences in their use for orthopedic surgery and ovariohysterectomy (Dohoo and Dohoo, 1996). Even so, there is particular concern about opioids and non-steroidal anti-inflammatory drug (NSAID) toxicity and their side effects in cats (Lascelles et al., 1999).

In fact, cats have an increased susceptibility to the toxic effects of NSAIDs because of a low capacity for hepatic glucuronidation, due to reduced hepatic UDP-glucuronosyltransferase (UGT) isoforms, which is the main pathway for NSAID metabolism in the liver (Court and Greenblatt, 2000), leading to a longer half-life in this species than in the dog (Taylor et al., 1996; Parton et al., 2000). However, these drugs are among the best analgesics for preventing and treating postoperative pain. They produce potent analgesic and anti-inflammatory effects, inhibit spinal nociceptive transmission and are indicated for the prevention and treatment of edema and inflammation, especially for musculoskeletal disorders (Lascelles et al., 2001).

The primary mode of action of NSAIDs is to inhibit cellular expression of COX (cyclooxygenase) enzymes in cell membranes (Vane, 1971). There are at least two COX isoforms. COX-1 is a constitutive form of the enzyme found in many tissues. It regulates normal

* Corresponding author. Address: Department of Surgery and Veterinary Anesthesiology, School of Veterinary Medicine and Animal Science, São Paulo State University, Distrito de Rubião Jr., s/n, 18600-000, UNESP Botucatu-SP, Brazil. Tel.: +1 6083955988.

E-mail address: pvms2001@yahoo.com.br (P.V.M. Steagall).

homeostasis by producing prostaglandins in the GI (gastrointestinal) mucosa, by regulating platelet aggregation, and by stimulating renal blood flow. The COX-2 isoform is constitutively expressed in a range of tissues and organs including ovarian and renal tissue. Its production is induced primarily by tissue damage since it is a pro-inflammatory inducible enzyme and is therefore, responsible for the production of other inducible enzymes which are consequently converted into various inflammatory mediators such as eicosanoids and other specific prostaglandin end-products. These mediators amplify nociceptive input and transmission to the spinal cord (Fu et al., 1990; Kujubu et al., 1991; Lees et al., 2004).

All NSAIDs inhibit both COX isoforms, suppressing the synthesis of homeostatic and pro-inflammatory prostaglandins, and consequently have a narrow therapeutic index. The primary side effects of this class of drugs are gastric irritation, development of protein-losing enteropathy, hepatic and renal damage, articular degradation and prolonged bleeding time by prevention of platelet aggregation (Mathews, 1996).

Carprofen is an NSAID of the arylpropionic acid class available as a racemic mixture. Its mode of action is not fully understood, however a recent study indicates that the drug has a preferential COX-2 inhibition, which tends to be lost at higher doses (Giraudel et al., 2005), while other studies indicate a weak inhibition of COX enzymes at therapeutic doses, which could explain the low incidence of side effects of the drug, since the inhibition of COX-2 results in the most common side effects observed with the use of NSAIDs (Taylor et al., 1996). Carprofen is approved for use in cats at 4 mg/kg in many countries (United Kingdom, France, Germany, The Netherlands, Italy, Belgium, Australia and New Zealand) for daily subcutaneous or intravenous administration. It is an effective analgesic for soft tissue and orthopedic procedures in cats and it is extensively used for perioperative analgesia in cats in the United Kingdom (Lascelles et al., 1995; Taylor et al., 1996; Balmer et al., 1998; Slingsby and Waterman-Pearson, 2000).

Although most of the NSAIDs are not licensed for chronic use in cats¹, some studies, reviews and text books suggest some “off-label” protocols using meloxicam (Lascelles et al., 2001; Wright, 2002; Robertson, 2005; Lascelles et al., 2007) and carprofen (Dobromylskyj et al., 2000; Wright, 2002) for pain management, but no studies have been performed to investigate the adverse effects of long term use of NSAIDs in cats. The aim of this study was to evaluate the adverse effects of the administration of subcutaneous carprofen over six days in healthy cats. Adverse effects on gastrointestinal, hematological or serum biochemical variables were investigated.

¹ In the United Kingdom, meloxicam has a market authorization for chronic use in the cat.

2. Materials and methods

The study was approved by the Animal Research Ethics Committee of the School of Veterinary Medicine and Animal Science, São Paulo State University, Botucatu, SP, Brazil.

2.1. Animals

Seven healthy domestic short hair adult cats were studied; three were male and four female weighing 3.4–3.7 kg. Before the study, a preliminary laboratory investigation (CBC – complete blood count and serum biochemical analyses) was performed to ensure that the cats were healthy. Haemoparasites were also investigated. The cats were dewormed with 600 mg of pirantel and praziquantel (Petzi Gatos, Vetbrands, Jacareí, SP, Brazil) and vaccinated against chlamidia psittacii, panleucopenia, calicivirus and feline rhinotracheitis (Feline-4, Merial Saúde Animal LTDA, Campinas, SP, Brazil). All cats were housed according to the Principles of the University Research Ethical Committee. Health checks were made at regular intervals between testing sessions. The cats were group housed and fed dry laboratory cat food. During testing, cats were housed individually in cages 80 cm high, 120 cm wide and 60 cm long. Cages were equipped with toys, a bed and a litter tray. All cats had been well handled and familiarized with the procedure for several weeks prior to the study.

2.2. Experimental protocol and drug treatment

The study comprised two 1-week treatment periods with a washout period of one month between successive treatments. A randomized cross-over study design was used, whereby each cat was each administered 2 treatments and served as its own control. All treatments were carried out for six days and were given between 12:00am and 1:00pm by the same investigator (FBM). Another blinded investigator (PVMS) performed a general daily health examination for any evidence of vomiting, diarrhea, signs of depression, inappetence, or signs of abdominal pain during the study.

Cats were given SID treatment with subcutaneous carprofen (Rimadyl; Pfizer Ltd., Sandwich, Kent, UK) 4 mg/kg (day 1), followed by 2 mg/kg (day 2 and 3) and 1 mg/kg (day 4 and 6) (CG) or 0.35 ml of saline (SG) as a drug-free negative control for six days. Cats did not receive any treatment on day 5. The volume of carprofen was made up to 0.35 ml with 0.9% saline to allow accurate dosing with a 1 mL syringe.

2.3. Anesthesia

On day –2, cats were weighed and then anaesthetized for their endoscopic evaluation and blood collection. Food but not water was withheld 12 h before anesthesia. Anesthesia was performed with 5 mg/kg ketamine (Vetaset, Fort-Dodge, Campinas, SP, Brazil) combined with 0.25 mg/kg of midazolam (Dormire, Cristália, Itapira,

SP, Brazil) and 0.01 mg/kg of buprenorphine (Temgesic, Schering-Plough, Rio de Janeiro, RJ, Brazil) in the same syringe, administered IM in the hind limb.

After clipping the antebrachium, a 24-gauge catheter (Angyocath, Beckton Dickinson, São Paulo, SP, Brazil) was aseptically inserted in a cephalic vein. If necessary, anaesthetic induction was completed with 1–2 mg/kg propofol IV (Propovan, Lab Cristália, Itapira, SP, Brazil) to achieve a plane of anesthesia sufficient for endotracheal intubation. Anaesthesia was maintained with isoflurane (Isothane, Baxter Health Care Corporation, Guayama, Puerto Rico, USA) in oxygen, administered through a circular breathing circuit. Lactated Ringer's solution was administered IV at 5 ml/kg/h throughout the endoscopic procedure.

2.4. Hematology procedures and serum biochemical analysis

Values for CBC, serum urea, protein, creatinine, ALT (alanine transaminase), ALP (alanine phosphatase), GGT (γ -glutamyl transferase), albumin, globulin and whole-blood platelet aggregation were measured before (day 2) and at seven days after SID treatment with subcutaneous carprofen or saline. Under general anesthesia, aseptic technique was used to place a 20-gauge 12 cm polyurethane jugular catheter (Angyocath, Beckton Dickinson, São Paulo, SP, Brazil) for collecting blood samples. The volume of blood collected was adjusted to be less than 10% of each cat's total blood volume and it was replaced with an equal volume of lactated Ringer's solution.

Blood (5 mL) was withdrawn from the jugular vein and one fraction was put into a glass tube containing EDTA (Vacutainer – Beckton Dickinson-BD, Franklin Lakes, USA) for CBC analysis and the other fraction was put into a tube without anticoagulant (Vacutainer – Beckton Dickinson, Franklin Lakes, USA) for serum biochemical analyses. All samples were analyzed within 2 h of collection. Serum urea, creatinine, ALT, ALP, and GGT activities were determined using reagent kits and a centrifugal auto-analyser (CELM Combate, Barueri, SP, Brazil).

A second sample (4 ml) of blood was collected and transferred to tubes containing sodium citrate dehydrate and citric acid for whole-blood platelet aggregation determination. Platelet aggregation was expressed in percentage and analyzed by the addition of ADP (adenosine diphosphatase) (ADP Reagent, Helena Laboratories, Beaumont, Texas, USA) to the plasma-rich platelets.

2.5. Endoscopy and lesion scoring

Endoscopy of the stomach and duodenum was performed in all cats on days –2 and 7 to ensure gastric integrity. Animals were placed in left lateral recumbency and a 1.0 m flexible endoscope was used. After completion of each endoscopy, suction was used to remove air from the stomach and esophagus.

Scoring lesions were graded according to Parton et al. (2000): Grade 0 (no visible hemorrhages, erosions, or ulcers); Grade 1 (1–5 punctate erosions, hemorrhages or both); Grade 2 (6–15 punctate erosions, hemorrhages or both); Grade 3 (16–25 punctate erosions, hemorrhages or both); Grade 4 (>25 punctate erosions, hemorrhages, or both, or 1–5 invasive erosions, or both); Grade 5 (>6 invasive erosions); and Grade 6 (ulcers of any size). All cats were Grade 0 before treatment. Erosion was defined as a <3 mm diameter discontinuation of the mucosa, and an ulcer as >3 mm with a craterous center. The veterinarian performing endoscopies (FQM) was unaware of the treatments received by the cats.

2.6. Statistical analysis

Statistical analysis was performed using commercial software (GraphPad Prism, GraphPad Software Inc., San Diego, CA). A paired *t*-test was used to investigate differences within and between treatments at each time point. Significance was set at $p < 0.05$.

3. Results

All cats completed the study without adverse clinical effects. Physical examinations revealed no clinical signs of vomiting, anorexia, diarrhoea, lethargy and weakness, or abdominal pain during the experiment. The cats' mean weight did not change between testing sessions (3.6 ± 0.2 kg – mean \pm standard deviation).

There were no changes in CBC, hemoglobin, hematocrit, total plasma protein, platelet count, whole-blood platelet aggregation, urea, creatinine and GGT from basal values to day 7, within or between groups at each time point, except that albumin values were lower at baseline (2.9 ± 0.2 g/dl) than on day 7 (3.2 ± 0.1 g/dl) (CG) and globulin and ALP were higher at baseline (2.8 ± 0.8 g/dl, 82.6 ± 31 U/L) than on day 7 (2.1 ± 0.6 g/dl, 45.3 ± 19 U/L) in CG and SG, respectively (Table 1). ALP values were lower in SG (45.3 ± 19 U/L) than in CG (57.6 ± 23 U/L) on day 7. All mean values (Table 1) were within reference ranges.

Serum ALT activity was increased at baseline in three carprofen-treated cats, and increased at baseline in three saline treated cats, but not on day 7 post-treatment. In both cases, they were not the same animals.

Gastric and duodenal endoscopic lesion scores in both groups were Grade 0 at both pre-treatment and on day 7, except that two cats in SG had grade 1 endoscopic lesion scores on day 7. This difference was not considered to be statistically significant.

4. Discussion

Anecdotal reports have indicated that NSAIDs have been used successfully in the treatment of chronic pain con-

Table 1
Mean \pm SD serum biochemistry variables and platelet aggregation in cats treated with carprofen or saline at baseline and at seven days after administration

		Urea (mg/dl)	Creatinine (mg/dl)	ALT activity (U/L)	ALP activity (U/L)	GGT activity (U/L)	Total protein (g/dl)	Globulin (g/dl)	Albumin (g/dl)	Platelet aggregation (%)
Carprofen	Baseline	48.5 \pm 6	1.2 \pm 0.1	41.9 \pm 10	112.2 \pm 77	3.1 \pm 1	5.7 \pm 0.8	2.8 \pm 0.8*	2.9 \pm 0.2	78 \pm 1
	Seven days	42.8 \pm 8	1.3 \pm 0.2	39.9 \pm 14	57.6 \pm 23	3.3 \pm 2	5.3 \pm 0.6	2.1 \pm 0.6	3.2 \pm 0.1*	73 \pm 1
Saline	Baseline	57.9 \pm 10	1.3 \pm 0.1	46.2 \pm 9	82.6 \pm 31*	3.8 \pm 2	5.6 \pm 0.3	2.6 \pm 0.5	3 \pm 0.4	73 \pm 1
	Seven days	49.8 \pm 13	1.3 \pm 0.1	36.1 \pm 10	45.3 \pm 19**	3.8 \pm 2	5.3 \pm 0.4	2.2 \pm 0.4	3.1 \pm 0.2	76 \pm 1

* Significant ($P < 0.05$) difference between baseline and at seven days.

** Significant ($P < 0.05$) difference between saline and carprofen at each time.

ditions in many cats, and some pain management reviews in cats have suggested “off-label” doses for meloxicam and carprofen (Dobromylskyj et al., 2000; Lascelles et al., 2001; Wright 2002; Robertson 2005; Lascelles et al., 2007). In such cases, subsequent treatments should be given at a reduced dose with an increased dose-interval taking into account the great inter-cat pharmacokinetics variability with the use of NSAIDs (Parton et al., 2000); which is how the dosing protocol was chosen for the present study (Taylor, personal communication). No attempt has been made to study the analgesic effects of this dosing schedule in the cat. However, this protocol has been used in clinical practice on a small number of cats undergoing surgery, none of which presented with any clinical side effects (Steagall, unpublished observations). In these cases, a complete CBC and biochemical analyses were performed prior to treatment and all cats were considered healthy. This is the first study done under laboratory conditions, focusing on the investigation of the side effects of long term use of NSAIDs in cats.

Administration of NSAIDs is the one of the most common predisposing factor causing gastroduodenal ulceration in dogs and cats. However, in most cases of ulceration, labeled doses and intervals have not been respected (Stanton and Bright, 1989; Jones et al., 1992; Runk et al., 1999; Lascelles et al., 2005). There is no data available describing the incidence of gastrointestinal side effects after NSAIDs administration in cats. In one study, endoscopy of five cats was performed before treatment and at 8 h post-treatment from a single dose of carprofen; however, no adverse effects were found (Parton et al., 2000).

Endoscopy is considered a sensitive method for detecting early NSAID-induced gastric injury. Gross endoscopic evaluation of gastric lesions correlates with gross lesions at necropsy and is therefore a reliable method of evaluating ulceration and gastric adverse effects in dogs (Dow et al., 1990). Dogs may show gastric lesions in endoscopy, even if they do not present any clinical signs from the side effects due to NSAID use (Luna et al., 2007). It would be reasonable to extrapolate these data to cats as well. None of the cats in the present study developed any endoscopic lesion but readers should be aware that the absence of side effects

may have been due to the small number of animals used in this study. This information cannot be extrapolated into a clinical setting in which patients typically undergo painful surgical procedures and may have other concurrent disease. In such circumstances, GI lesions may be exacerbated and result in clinical consequences.

Carprofen is considered to be an effective analgesic for postoperative analgesia in cats (Lascelles et al., 1995; Balmer et al., 1998; Slingsby and Waterman-Pearson, 2000; Mollenhoff et al., 2005). The mechanism of action of carprofen is not fully understood but its weak inhibition of COX-2 is associated with a reduction of side effects, therefore, it could be a useful analgesic in this species (Lascelles et al., 1995; Taylor et al., 1996). For example, in a clinical trial, the administration of 4 mg/kg of subcutaneous carprofen (day 1) followed by 1.3 mg/kg every 8 h (days 2–5) did not cause clinical adverse effects in cats undergoing orthopedic surgery and showed superior antinociceptive activity than levomethadone and buprenorphine (Mollenhoff et al., 2005). However, there is a report of duodenal perforation in a cat caused by the administration of oral carprofen followed by flunixin meglumine and dexamethasone (Runk et al., 1999). A recent review mentions anecdotal reports of carprofen toxicity, generally associated with concurrent and prolonged administration of the oral formulation (Lascelles et al., 2007). In the present study, subcutaneous administration of carprofen did not cause clinical adverse effects.

Renal function was assessed by measuring serum urea and creatinine concentrations as done in previous studies (Lascelles et al., 1995; Balmer et al., 1998; Parton et al., 2000), and no differences were found between saline and carprofen-treated cats. These concentrations can be used on their own to evaluate renal function, but are not highly sensitive markers of decreased renal function as they only increase when more than 75% of renal function has been compromised, in the case of severe renal damage, and therefore are not reliable for early diagnosis of renal failure (Raekallio et al., 2006). Glomerular filtration rate and renal scintigraphic imaging are the gold-standard tests for renal insufficiency and nephropathies, even in early stages (Raekallio et al., 2006). Acute renal damage is more likely

to result from NSAID use in animals which already have compromised renal function, are hypotensive during anesthesia or are dehydrated during anesthesia (Mathews et al., 1990). In a recent survey, almost 50% of the cats that were referred for acute renal failure were considered NSAIDs related, however none of the cats had been treated with carprofen or meloxicam (Pages, 2005). Thus, it seems that the incidence of acute renal failure associated with NSAID use is uncommon; however veterinarians should perform renal function tests prior to administration of repeated doses of NSAIDs (Lascelles et al., 2007).

In general, carprofen had no effect on serum liver enzyme activity; however, the number of cats used in this study was too low to draw a proper conclusion. Other studies have not been able to detect hepatotoxic effects after use of a single dose of carprofen in cats (Parton et al., 2000). Hepatocellular toxicosis has been reported in dogs after carprofen administration (MacPhail et al., 1998) but not in the cat. ALP values were lower in SG than in CG on day 7 but all mean values were within reference range.

Primary hemostasis is mediated by the interaction between the vascular endothelium and platelets. Inhibition of COX-1 activity by non-selective NSAIDs decreases thromboxane A2 formation and therefore can reduce blood platelet aggregation disturbing or even inhibiting primary hemostasis (Fresno et al., 2005). In this study, platelet count and blood platelet aggregation values were not altered during carprofen administration. Results suggest that carprofen did not impair primary hemostasis in healthy cats.

If veterinarians wish to prescribe “off-label” dosages of NSAIDs for long term use, this should be performed with owner’s written consent, who must be informed about the possible side effects as well as the kinds of adverse clinical signs they should look for. Special attention must be paid to the development of clinical signs of toxicity and rapid and appropriate action should be taken when necessary (Lascelles et al., 2007). The benefits derived from NSAID usage have to be balanced with the known toxic effects. A complete CBC and serum biochemical analysis must be performed before and during treatment to monitor adverse effects.

5. Conclusions

Administration of carprofen did not result in clinically important adverse effects and was well tolerated in seven healthy adult cats. These results may not necessarily apply to the entire target population. Further studies measuring the pharmacokinetics of carprofen in the cat throughout the distribution and elimination phases are needed to confirm the suitability of this protocol for repeat dosing as used in this study.

References

- Balmer, T.V., Irvine, D., Jones, R.S., Roberts, M.J., Slingsby, L., Taylor, P.M., Waterman, A.E., Waters, C., 1998. Comparison of carprofen and pethidine as postoperative analgesics in the cat. *Journal of Small Animal Practice* 39, 158–164.
- Court, M., Greenblatt, D., 2000. Molecular genetic basis for deficient acetaminophen glucuronidation by cats: UGT1A6 is a pseudogene, and evidence for reduced diversity of expressed hepatic UGT1A isoforms. *Pharmacogenetics* 10, 355–369.
- Dobromylskij, P., Flecknell, P.A., Lascelles, B.D., Livingston, A., Taylor, P.M., Waterman-Pearson, A.E., 2000. *Pain Management in Animals*. WB Saunders, London, pp. 53–79.
- Dohoo, S.E., Dohoo, I.R., 1996. Postoperative use of analgesics in dogs and cats by Canadian veterinarians. *The Canadian Veterinary Journal* 37, 546–551.
- Dow, S.W., Rosychuk, R.A., McChesney, A.E., Curtis, C.R., 1990. Effects of flunixin and flunixin plus prednisone on the gastro-intestinal tract of dogs. *American Journal of Veterinary Research* 51, 1131–1138.
- Fresno, L., Moll, J., Peñalba, B., Espada, Y., Andaluz, A., Prandi, D., Gopegui, R.R., Garcia, F., 2005. Effects of preoperative administration of meloxicam on whole blood platelet aggregation, buccal mucosal bleeding time, and haematological indices in dogs undergoing elective ovariohysterectomy. *The Veterinary Journal* 170, 138–140.
- Fu, J.Y., Masferrer, J.L., Seibert, K., Raz, A., Needleman, P., 1990. The induction and suppression of prostaglandin H2 synthase (cyclooxygenase) in human monocytes. *Journal of Biological Chemistry* 265, 16737–16740.
- Giraudel, J.M., Toutain, P.L., Lees, P., 2005. Development of in vitro assays for the evaluation of cyclooxygenase inhibitors and predicting selectivity of nonsteroidal anti-inflammatory drugs in cats. *American Journal of Veterinary Research* 66, 700–709.
- Hewson, C.J., Dohoo, I.A., Lemke, K.A., 2006. Perioperative use of analgesics in dogs and cats by Canadian veterinarians in 2001. *The Canadian Veterinary Journal* 47, 352–359.
- Jones, R.D., Baynes, R.E., Nimitz, C.T., 1992. Nonsteroidal anti-inflammatory drug toxicosis in dogs and cats: 240 cases (1989–1990). *Journal of the American Veterinary Medical Association* 201, 475–477.
- Kujubu, D.A., Fletcher, B.S., Varnum, B.C., Lim, R.W., Herschman, H.R., 1991. TIS10, a phorbol ester tumor promoter-inducible mRNA from Swiss 3T3 cells, encodes a novel prostaglandin synthase/cyclooxygenase homologue. *Journal of Biological Chemistry* 266, 12866–12872.
- Lascelles, B.D.X., Cripps, P., Mirchandani, S., Waterman, A.E., 1995. Carprofen as an analgesic for postoperative pain in cats: dose titration and assessment of efficacy in comparison to pethidine hydrochloride. *Journal of Small Animal Practice* 36, 535–541.
- Lascelles, B.D.X., Capner, C.A., Waterman-Pearson, A.E., 1999. Current British veterinary attitudes to perioperative analgesia for cats and small mammals. *The Veterinary Record* 145, 601–604.
- Lascelles, B.D., Henderson, A.J., Hackett, I.J., 2001. Evaluation of the clinical efficacy of meloxicam in cats with painful locomotor disorders. *Journal of Small Animal Practice* 42, 587–593.
- Lascelles, B.D.X., Bliklager, A.T., Fox, S.M., Reece, D., 2005. Gastro-intestinal tract perforation in dogs treated with a selective cyclooxygenase-2 inhibitor: 29 cases (2002–2003). *Journal of the American Veterinary Medical Association* 227, 1112–1117.
- Lascelles, B.D.X., Court, M.H., Hardie, E.H., Robertson, S.A., 2007. Nonsteroidal anti-inflammatory drugs in cats: a review. *Veterinary Anaesthesia and Analgesia* 34, 228–250.
- Lees, P., Landoni, M.F., Giraudel, J., Toutain, P.L., 2004. Pharmacodynamics and pharmacokinetics of non-steroidal anti-inflammatory drugs in veterinary species. *Journal of Veterinary Pharmacology and Therapeutics* 27, 479–490.
- Luna, S.P.L., Basílio, A.C., Steagall, P.V.M., Machado, L.P., Moutinho, F.Q., Takahira, R.K., Brandão, C.V.S., 2007. Evaluation of adverse effects of long-term oral administration of carprofen, etodolac, flunixin meglumine, ketoprofen and meloxicam in dogs. *American Journal of Veterinary Research* 68, 258–264.
- MacPhail, C.M., Lappin, M.R., Meyer, D.J., Smith, S.G., Webster, C.R., Armstrong, P.J., 1998. Hepatocellular toxicosis associated with the use

- of carprofen in 21 dogs. *Journal of the American Veterinary Medical Association* 212, 1895–1901.
- Mathews, K.A., 1996. Nonsteroidal anti-inflammatory analgesics in pain management in dogs and cats. *The Canadian Veterinary Journal* 37, 539–545.
- Mathews, K.A., Doherty, T., Dyson, D.H., 1990. Nephrotoxicity in dogs associated with methoxyflurane anesthesia and flunixin meglumine analgesia. *The Canadian Veterinary Journal* 31, 766–771.
- Mollenhoff, A., Nolte, I., Kramer, S., 2005. Anti-nociceptive efficacy of carprofen, levomethadone and buprenorphine for pain relief in cats following major orthopaedic surgery. *Journal of Veterinary Medicine A: Physiology, Pathology, Clinical Medicine* 52, 186–198.
- Pages, J.P., 2005. Néphropathies dues aux anti-inflammatoires non-steroidiens (AINS) chez le Chat: 21 observations (1993–2001). *Pratique médicale & chirurgicale de l'animal de compagnie* 40, 177–181.
- Parton, K., Balmer, T.V., Boyle, J., Whittam, T., Machon, R., 2000. The pharmacokinetics and effects of intravenously administered carprofen and salicylate on gastrointestinal mucosa and selected biochemical measurements in healthy cats. *Journal Veterinary of Pharmacology and Therapeutics* 23, 73–79.
- Raekallio, M.R., Hielm-Bjorkman, A.K., Kejonen, J., Salonen, H.M., Sankari, S.M., 2006. Evaluation of adverse effects of long-term orally administered carprofen in dogs. *Journal of the American Veterinary Medical Association* 228, 876–880.
- Robertson, S.A., 2005. Managing pain in feline patients. *Veterinary Clinics of North America (Small Animal Practice)* 35, 129–146.
- Runk, A., Kyles, A.E., Downs, M.O., 1999. Duodenal perforation in a cat following the administration of nonsteroidal anti-inflammatory medication. *Journal of the American Animal Hospital Association* 35, 52–55.
- Slingsby, L.S., Waterman-Pearson, A.E., 2000. Postoperative analgesia in the cat after ovariohysterectomy by use of carprofen, ketoprofen, meloxicam or tolfenamic acid. *Journal of Small Animal Practice* 41, 447–450.
- Stanton, M.E., Bright, R.M., 1989. Gastrointestinal ulceration in dogs: retrospective study of 43 cases in literature review. *Journal of Veterinary Internal Medicine* 3, 238–244.
- Taylor, P.M., Delatour, P., Landoni, F.M., Deal, C., Pickett, C., Shojaee Aliabadi, F., Foot, R., Lees, P., 1996. Pharmacodynamics and enantioselective pharmacokinetics of carprofen in the cat. *Research in Veterinary Science* 60, 144–151.
- Vane, J.R., 1971. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature: New Biology* 23, 232–235.
- Wright, B.D., 2002. Clinical pain management techniques for cats. *Clinical Techniques in Small Animal Practice* 17, 151–157.