Carprofen

Mark A. Mitchell DVM, MS, PhD

Antiinflammatory compounds are routinely used in veterinary medicine to manage traumatic injuries, provide analgesia, alter glucose metabolism, control allergies, and treat a variety of disease presentations. Historically, steroidal antiinflammatory agents were used to manage the majority of the cases described above; however, these compounds have lost favor in veterinary medicine because of their potential side effects. One significant concern limiting their use relates to their negative effect on the immune system. The potential immunosuppressive action associated with steroidal antiinflammatories include the suppression of T-lymphocytes, limiting the migration of inflammatory cells, the reduction of chemotaxins, and decreased antigen processing.[1]

Nonsteroidal antiinflammatory drugs (NSAIDs) do not produce the same negative immunosuppressive effects and are finding greater acceptance in veterinary medicine. The NSAIDs are not only being used to provide antiinflammatory properties, but analgesic and antipyretic properties too. These compounds are generally thought to work by inhibiting the synthesis of prostaglandins, cyclooxygenase, and phospholipase A_2. Their effectiveness varies depending on how well they inhibit the inflammatory response.

Carprofen is a nonsteroidal antiinflammatory compound that is licensed for use in dogs with osteoarthritis and as a postoperative analgesic. This NSAID is from the propionic acid class, which includes ibuprofen, ketoprofen, and naproxen. Carprofen is soluble in alcohol, but practically insoluble in water. The mechanism of action of this compound is likely attributed to the inhibition of cyclooxygenase (COX) activity. There are two different COX enzymes that have been described in mammals: COX-1 and COX-2. Historically, compounds with activity against COX-1 enzymes were believed to affect the synthesis of prostaglandins important to normal gastrointestinal and renal function, while inhibition of COX-2 enzymes were solely associated with altering antiinflammatory activity. However, more recent work suggests that the activity of the enzymes is not that well delineated.[2] The identification of selective COX-2 inhibitors has become a primary concern for pharmaceutical companies, as these compounds are less likely to induce the negative side effects associated with COX-1 inhibition. Wilson and coworkers[3] found carprofen to be five times more selective for COX-2 inhibition compared with COX-1 activity in different canine tissues, while Kay-Mugford and coworkers[4] found that carprofen was only 1.75 times more selective for COX-2 than COX-1 using a canine DH82 monocyte/macrophage cell line. Kay-Mugford and coworkers[4] also reported that meloxicam, another NSAID, inhibited COX-2 activity twelve times more effectively than COX-1 in the cell line.

In dogs, carprofen is well absorbed via the gastrointestinal tract, and peak levels are achieved within a few hours.[1] This drug is metabolized by the liver, and primarily excreted via the feces. A small percentage of the drug is excreted via the urine.

Carprofen is primarily used to manage pain in dogs. A study evaluating the clinical efficacy of carprofen, meloxicam, and a neutraceutical found that carprofen and meloxicam both had an effect on ground reaction forces in affected joints, but only dogs treated with meloxicam had a full return to normal.[5] Horstman and coworkers[6] found that dogs given carprofen following cranial cruciate sur-

From the School of Veterinary Medicine, Department of Veterinary Clinical Sciences, Louisiana State University, Baton Rouge, LA 70803 USA

Address correspondence to: Dr. Mark Mitchell, School of Veterinary Medicine, Department of Veterinary Clinical Sciences, Louisiana State University, Baton Rouge, LA 70803. E-mail: mitchell@vetmed.lsu.edu.

1055-937X/05/1401-00089$30.00
doi:10.1053/j.saep.2005.12.010

gery had improved limb function postoperatively, although the difference was not statistically different. The authors used 20 dogs for the experimental trial, and a power analysis suggested that 35 animals would have been necessary to detect the differences in the study group. Although the difference in response postoperatively was not significantly different, the carprofen did appear to provide some benefit to the dogs postoperatively. In a study evaluating the effect of perioperative carprofen on postoperative pain in dogs undergoing a cranial cruciate repair surgery, there was no difference in the measures used to assess pain between the two groups.[7] The authors suggested that the measures used to assess pain in the two groups were not sensitive enough to detect differences if they existed.

Although not approved for cats, carprofen has been used to manage pain postoperatively in feline cases. There were no measureable differences in pain or sedation scores between cats given carprofen (4 mg/kg) or meloxicam (0.3 mg/kg).[8] Parton and coworkers[9] also reported no significant differences in the endoscopic examination of the stomach or duodenum, or hematologic and serum biochemistry values in cats given carprofen (4 mg/kg).

The side effects associated with carprofen in mammals are primarily associated with the gastrointestinal and hematopoietic systems. Gastric side effects are a concern when using carprofen long term. Although carprofen is more selective for COX-2 activity, the potential for COX-1 selection is a concern. Guerios and coworkers[10] evaluated the potential gastric side effects of long-term carprofen administration in canines. Dogs were given 2.2 mg/kg carprofen for 30 days. Gastroscopic examination of the dogs did not reveal any negative side effects. Hematologc side effects are another concern associated with carprofen. When Labrador retrievers were given 2.2 mg/kg carprofen, there were mild, nonsignificant alterations in the hematologic and serum biochemistries.[11] One exception was a delayed platelet aggregation. Although NSAIDs have been associated with alterations in capillary bleeding times, there was no significant difference in this measurement in dogs given 4 mg/kg carprofen.[12] Hepatic side effects were reported in 21 dogs after receiving carprofen (1.57-3.1 mg/kg) orally every 12 hours for 3 to 180 days.[13] Affected dogs were anorectic, vomited, had diarrhea, and in some cases developed renal tubular disease. Improvement was noted in most of the dogs after the drug was discontinued.

Whereas there has been a significant amount of work evaluating the effects of carprofen in dogs, there are relatively few studies evaluating this drug in avian and exotic species. To date, there have only been carprofen studies in rats and poultry. Even in the absence of legitimate research, carprofen remains a popular NSAID in avian and exotic medicine.

Rats are commonly used as research animals and kept as pets. Because these animals are routinely used for surgical procedures in research, there is a need for appropriate analgesic compounds. Pet rats are also routinely presented for surgical procedures, including castration, ovariohysterectomy, and mass removal, and therefore would also benefit from the administration of analgesics. Characterizing pain in rats can be difficult, as these animals can be stoic. Liles and Flecknell[14] evaluated the effectiveness of several analgesics in rats postoperatively. Based on a belief that depression in food and water consumption may be associated with the presence of postoperative pain, the authors tested the hypothesis that rats offered analgesics, such as carprofen, would be less likely to have decreased food and water consumption postoperatively. The authors found that rats provided carprofen following a laporotomy procedure were less likely to have depressed food and water consumption than those controls offered saline.

Surgical procedures can be associated with significant postoperative morbidity. Flecknell and coworkers[15] found that rats not provided analgesia lost approximately 3% of their body weight. The weight loss was attributed to a reduction in the consumption of food and water. Rats given carprofen orally were less likely to have reduced water consumption in comparison, but did still reduce their water consumption by 13%. Rats given carprofen subcutaneously did not experience any reduction in water consumption.

Carprofen is routinely used to provide analgesia in exotic pet mammals. The current dosing regimens are primarily based on the results of the studies performed on rats (Table 1). Because our understanding of this drug is limited, it is important to use caution when dosing different species of rodents, marsupials, lagomorphs, and carnivores.

Studies evaluating the analgesic properties of carprofen in birds are limited to poultry. Danbury and coworkers[16] evaluated the effectiveness of providing carprofen in the diet of broilers, and found that plasma concentrations were linearly

Table 1. Carprofen Dosages for Exotic and Avian Species

Class	Dose
Avian	5-10 mg/kg PO[20]
Ferrets	1 mg/kg PO q12-24h[21]
	4 mg/kg IM, SC q24h[22]
Rodents	4 mg/kg SC q24h (chinchillas)[23]
	5-10 mg/kg PO[14]
Rabbits	2.2 mg/kg PO q24h[24]
	4 mg/kg SC, q24h[22]
Reptiles	1-4 mg/kg PO, SC, IM, IV[18]
	2-4 mg/kg PO, SC, IM q24-72h[19]

correlated to the amount of food that the birds consumed. In addition, lame birds were more likely to selectively consume the diet with the drug than sound broilers, and birds with a lameness improved when fed a diet supplemented with carprofen. Carprofen was also found to shorten the time required for broilers with lameness to traverse an obstacle course.[17] Healthy birds completed the course in 11 seconds, while lame birds receiving no treatment completed the course in 34 seconds. The administration of carprofen to the lame birds shortened the time required to 18 seconds.

To date, there have been no studies to evaluate the efficacy of carprofen in psittacines, although it is routinely used to manage pain. Current dosing regimens are consistent with mammalian doses (Table 1). The positive results reported in poultry suggest that this drug may prove useful in psittacines.

Lawton[18] and Redrobe[19] recommended dosing reptiles with 1 to 4 mg/kg and 2 to 4 mg/kg, respectively (Table 1). The dosing interval at these concentrations was 24 to 72 hours.[19] It is important to consider that these recommendations are anecdotal, as there have been no studies done to determine the pharmacokinetics of these drugs in reptiles. When using carprofen in reptiles, it is important to evaluate these patients for the same potential side effects described in mammals.

Conclusion

With the advent of new compounds, there is always the desire to evaluate them in new species. Unfortunately, the majority of these compounds will be used anecdotally, as there are limited resources to thoroughly investigate these drugs in avian and exotic species. Veterinarians prescribing these compounds should address the off-label usage of these drugs and their potential side effects with their clients. Veterinarians should also share their experiences with other veterinarians by publishing any available data so that a safe, albeit anecdotal, dosing regimen can be developed. The recommended doses for avian and exotic species found in Table 1 appear to be based on this concept.

References

1. Plumb D: Glucocorticoids, in Veterinary Drug Handbook, 4th edition. (ed) Donald C. Plumb, Ames, IA, Iowa State Press, pp 387-389, 2002
2. Hawkins MG, Machin KL: Avian pain and analgesia. Proc Assoc Avian Vet, New Orleans, LA, pp 165-174, 2004
3. Wilson JE, Chandrasekharan NV, Westover KD, Eager KB, Simmons DL: Determination of expression of cyclooxygenase −1 and −2 isoenzymes in canine tissue and their differential sensitivity to nonsteroidal anti-inflammatory drugs. Am J Vet Res 65(6):810-818, 2004
4. Kay-Mugford P, Benn SJ, LaMArre J, Conlon P: In vivo effects of nonsteroidal anti-inflammatory drugs on cyclooxygenase activity in dogs. Am J Vet Res 61(7):802-810, 2000
5. Moreau M, Dupuis J, Bonneau NH, Desnoyers M: Clinical evaluation of a neutraceutical, carprofen and meloxicam for the treatment of dogs with osteoarthritis. Vet Record 152(11): 323-329, 2003
6. Horstman CL, Conzemius MG, Evans R, Gordon WJ: Assessing the efficacy of perioperative oral carprofen after cranial cruciate surgery using noninvasive, objective pressure platform gait analysis. Vet Surg 33(3):286-292, 2004
7. Gaynor JS, Brevard S, Mallinckrodt C, Baker G, Wander K: Effect of perioperative pain in dogs undergoing surgery for stabilization of ruptured cranial cruciate ligaments. Vet Therapeut 3(4): 425-434, 2002
8. Slingsby LS, Waterman-Pearson AE: Comparison between meloxicam and carprofen for post-operative analgesia after feline ovariohysterectomy. J Sm Anim Pract 43(7):286-289, 2002
9. Parton K, Balmer TV, Boyle J, Whittem T, Machon R: The pharmacokinetics and effects of intravenously administered carprofen and salicylate on gastrointestinal mucosa and selected biochemical measurements in healthy cats. J Vet Pharmacol Therap 23(2):73-79, 2000
10. Guerios SD, Sprea G, Deconto I, Okar RG: Gastroscopic examination after oral administration of nonsteroidal anti-inflammatory agents in dogs. Arch Vet Science 7(2):53-58, 2002
11. Hickford FH, Barr SC, Erb HN: Effect of carpro-

fen on hemostatic variables in dogs. Am J Vet Res 62(10):1642-1646, 2001
12. Redin M: Capillary bleeding time in anesthetized dogs given carprofen. Dansk veterinaer 83(13): 13-14, 2000
13. MacPhail CM, Lappin MR, Meyer DJ, Smith SG, Webster CRL, Armstrong PJ: Hepatocellular toxicosis associated with administration of carprofen in 21 dogs. JAVMA 212(12):1895-1901, 1998
14. Liles JH, Flecknell PA: A comparison of the effects of buprenorphine, carprofen and flunixin following laporotomy in rats. J Vet Pharmacol Therap 17(4):284-290, 1994
15. Flecknell PA, Orr HE, Rougham JV, Stewart R: Comparison of the effects of oral or subcutaneous carprofen or ketoprofen in rats undergoing laparotomy. Vet Record 144(3):65-67, 1999
16. Danbury TC, Weeks CA, Chambers JP: Self-selection of the analgesic drug carprofen by lame broiler chickens. Vet Record 146(11):307-311, 2000
17. McGeown D, Danbury TC, Waterman-Pearson AE, Kestin SC: Effect of carprofen on lameness in broiler chickens. Vet Record 144(24):668-671, 1999
18. Lawton MPC: Pain management after surgery. Proc N Am Vet Conf: 782, 1999
19. Redrobe S: Anesthesia and analgesia, in Girling SJ, Raiti P (eds), BSAVA Manual of Reptiles. Gloucester, England, British Small Animal Veterinary Association, pp131-146, 2004
20. Lawton MPC: Anesthesia, in: Beynon PH, Forbes NA, Harcourt-Brown NH (eds), BSAVA Manual of Raptors, Pigeons and Waterfowl. Ames, IA, Iowa State University Press, pp 79-88, 1996
21. Brown SA: Ferret drug dosages, in Antinoff N, Bauck L, Boyer TH (eds): Exotic Formulary. Lakewood, CO, AAHA Press, 1999, pp 43-61, 1999
22. Heard DJ: Anesthesia, analgesia, and sedation of small animals, in Quesenberry KE, Carpenter JW (eds). Ferrets, Rabbits, and Rodents Clinical Medicine and Surgery, 2nd ed. St. Louis, MO, Saunders, pp 356-369, 2004
23. Richardson VCG: Chinchillas: Anesthesia and drug treatments, in Sutton JB, Swift ST (eds), Diseases of Small Domestic Rodents. Malden MA, Blackwell Science Publications, pp 40-51, 1997
24. Paul-Murphy J, Ramer C: Urgent care of the pet rabbit. Vet Clinics N Am Ex An Pract 1:127-152, 1998