Comparative Medicine
Copyright 2020
by the American Association for Laboratory Animal Science

Vol 70, No 1
February 2020

Letter to the Editor

Dear Editors,

I would like to address what appears to be a significant omission regarding the use of ketoprofen for pain management in rat described in the article entitled "Clinical Management of Pain in Rodents" published in the December 2019 issue of Comparative Medicine.[2] Table 13, labeled "Updated analgesic dosing recommendations" was modified from a table included in an article written by Paul Flecknell.[1] This table includes the use of ketoprofen for rat at a dose of 5 mg/kg, SC, Q24. The Flecknell article also cites the study by Shientag and colleagues,[3] which found that a single 5 mg/kg of ketoprofen, administered SC, resulted in significant gastrointestinal toxicity in rat including bleeding, erosions and ulcers. By omitting a description or discussion of the Shientag report, readers may not be fully informed as to the risk involved using ketoprofen in rat. This omission should be addressed, since the Foley and colleagues article will likely be widely accessed for information regarding medical management of pain in rodents.

Lisa J Shientag, VMD, DACLAM
University of Massachusetts Medical School, MA

References

1. **Flecknell P.** 2018. Rodent analgesia: Assessment and therapeutics. Vet J **232:**70–77.
2. **Foley PL, Kendall LV, Turner PV.** 2019. Clinical management of pain in rodents. Comp Med **69:**468–489.
3. **Shientag LJ, Wheeler SM, Garlick DS, Maranda LS.** 2012. A therapeutic dose of ketoprofen causes acute gastrointestinal bleeding, erosions, and ulcers in rats. J Am Assoc Lab Anim Sci **51:**832–841.

Response to Dr Shientag's Letter to the Editor:

Thank you for the opportunity to respond to Dr Shientag's letter and comments on our manuscript, "Clinical Management of Pain in Rodents".[2] Dr Shientag kindly refers to a published study performed by her and others where a single dose of ketoprofen at 5 mg/kg SC caused gastrointestinal bleeding, mucosal erosions, and ulcers in the small intestinal tract of female Sprague–Dawley rats. Indeed, in the publication, it stated that the dose of 5 mg/kg was chosen based on other publications showing this to be a safe and effective dose.[1,3] Omission of Dr Shientag's data in our own review was an oversight. While we conducted a thorough literature review, undoubtedly, we missed one or more papers or case reports including this one. In Dr Shientag's study, rats were necropsied 24 h after a single dose, with or without isoflurane anesthesia. Notable findings were presence of fecal occult blood, and decreases in PCV and total protein. No grossly observable mucosal alterations were observed in any rats and there were no reported clinical signs of illness or morbidity; however mucosal lesions were evident from histopathology. This raises the likelihood that subclinical adverse effects may be occurring in rats administered ketoprofen at 5 mg/kg but that in most cases, rats recover uneventfully.

Dr Shientag is absolutely correct that precautions must be taken when administering NSAIDS to rodents, in particular those that are not cyclooxygenase-2 (Cox2) specific such as ketoprofen. The concerns for adverse events must certainly be weighed against the benefits of using a dose that is sufficient to provide effective analgesia. The safety margin is limited in these drugs especially if repeat doses are administered. Our discussion on side effects (see page 483) warns readers about the unintended side effects of NSAIDS including gastric and duodenal ulcers and intestinal perforations in more extreme cases.[5] We also specifically noted that adverse effects can be seen even at recommended doses (e.g. the example of banamine-induced renal injury). We further provide a footnote to Table 13 with the caveat that "caution should be taken with higher doses of NSAIDS" and that multimodal analgesia is recommended. This low margin of safety with NSAIDS is not restricted to just rodent species as noted by Sostres and colleagues.[4]

NSAIDS remain an important pharmaceutical tool for pain management. We agree with Dr Shientag that these drugs pose risks, and that dosages must be carefully selected to consider both analgesic efficacy and potential side effects. Cox2 specific inhibitors are preferable for their lower potential for adverse impact, and multimodal regimens should be used when possible to allow use of lower doses.

Patricia L Foley, DVM, DACLAM
Georgetown University, Washington, DC

Lon V Kendall, DVM, DACLAM
Colorado State University, Fort Collins, CO

Patricia V Turner, DVM, DACLAM
Charles River, Wilmington, MA
University of Guelph, Canada

References

1. **Flecknell PA, Orr HE, Roughan JV, Steward R.** 1999. Comparison of the effects of oral or subcutaneous carprofen or ketoprofen in rats undergoing laparotomy. Vet Rec **144:**65–67**.**
2. **Foley PL, Kendall LV, Turner PV.** 2019. Clinical management of pain in rodents. Comp Med **69:**468–489.
3. **Roughan JV, Flecknell PA.** 2001. Behavioural effects of laparotomy and analgesic effects of ketoprofen and carprofen in rats. Pain **90:**65–74.
4. **Sostres C, Gargallo CJ, Lanas A.** 2013. Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. Arthritis Res Ther **15 (Suppl 3):**S3.
5. **Wallace JL, McKnight W, Reuter BK, Vergnolle N.** 2000. NSAID-induced gastric damage in rats: requirement for inhibition of both cyclooxygenase 1 and 2. Gastroenterology **119:**706–714.