Review of the Indications and Regulatory Considerations for the Use of Ketoprofen in Horses

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Ketoprofen is a nonsteroidal anti-inflammatory drug approved for use in horses. It has a long duration of effect but a relatively rapid clearance from the plasma. These and other pharmacodynamic and pharmacokinetic characteristics of ketoprofen have important implications to practitioners to maximize the benefits of its use and to racing and show officials who must regulate its use. Authors' address: Equine Analytical Chemistry Laboratory, California Veterinary Diagnostic Laboratory System, University of California at Davis, Davis, CA 95617. © 1997 AAEP.

1. Introduction
Ketoprofen [(±)-2(3-benzoylphenyl)propionic acid] is an anti-inflammatory drug (NSAID) approved by the Food and Drug Administration for use in horses for the alleviation of inflammation and pain associated with musculoskeletal disorders. It is a member of the propionic acid class of NSAID’s, which includes ibuprofen, naproxen, and fenoprofen. The recommended intravenous dose of ketoprofen for horses is 2.2 mg/kg of body weight (BWT) once a day for a maximum of 5 consecutive days. A thorough and careful review of the scientific veterinary literature provides practitioners with logical and practical guidance as to the most beneficial use of ketoprofen in horses. In addition, the results of many of these studies indicate that there are pharmacological characteristics of ketoprofen that are of particular interest to regulatory officials in the racing and show industries.

2. Results
A. Efficacy in Clinical Models
The efficacy of ketoprofen compared with other NSAID’s to alleviate musculoskeletal inflammation and pain in horses has been examined in a number of studies with equivocal results. For example, in several carpal synovitis models, ketoprofen was found to be equivalent to the NSAID flunixin, but less effective than the NSAID phenylbutazone, at relieving the signs of inflammation.1 In a chronic laminitis model, however, ketoprofen, at a higher than recommended dose (3.63 mg/kg BWT), was shown to be more effective than phenylbutazone (4.4 mg/kg BWT) and to be significantly effective at relieving pain for up to 24 h.2 The explanation for the variable results of these studies is unclear, but they are consistent with the results of studies in other species, including humans. Practitioners may find
that the response to ketoprofen may vary with the individual patient and the condition being treated. Also of significance to practitioners are the results of a study involving several NSAID’s that found that ketoprofen caused the fewest adverse effects in horses when all of the drugs were administered at doses higher than the manufacturers’ recommendations.3

B. Mechanism of Action
The effects of NSAID’s have traditionally been ascribed to their inhibitory action on cyclo-oxygenase enzymes. Multiple studies have shown that ketoprofen can inhibit the formation of thromboxanes and prostaglandins in the horse, as both are products of the cyclo-oxygenase pathway.4,5 Evidence can also be found in several studies that NSAID’s, including ketoprofen, can cause a rebound effect on cyclo-oxygenase activity following withdrawal of the agent.4,5 The clinical significance of these findings has not been explored, but further study may be warranted.

The results of recent studies on a number of NSAID’s, including ketoprofen, indicate that these compounds may have effects on inflammatory pathways other than cyclo-oxygenase. For example, there is evidence that ketoprofen, as well as flunixin, can inhibit bradykinin-induced swelling.4 These findings may help explain the differences in clinical effectiveness between NSAID’s, independently of their potency to inhibit cyclo-oxygenase. Ketoprofen has also been shown to inhibit rabbit neutrophil and human lung lipoxygenase activity. The results of other studies, however, have failed to confirm an inhibitory effect on lipoxygenase in the horse.4,5

C. Pharmacokinetic Parameters
The pharmacokinetics of ketoprofen in horses has been well described. As a chiral compound ketoprofen exists as two enantiomers, S(+) and R(−)KTP, though currently only the racemic mixture is available as a commercial product. There is evidence that in the horse the R(−) enantiomer is cleared more rapidly than the S(+) enantiomer, but the clinical significance of this finding has not been determined.6 The results of most studies indicate that the plasma half-life of the racemic mixture is approximately 1.3 h.7 In contrast, the plasma half-life of flunixin is over twice as long at approximately 3.4 h.1 The half-life of ketoprofen in inflammatory exudate, however, is much longer.1 This may explain, in part, its long duration of action, despite a short plasma half-life. Clearance of ketoprofen appears to be primarily by renal excretion of both the unchanged parent compound and a base-labile conjugate.7 A large portion of the administered dose, however, was not accounted for by total renal excretion.7 The pharmacokinetics of ketoprofen did not significantly change with repeated administrations over 5 days, which is the maximum duration of treatment recommended by the manufacturer.7 Therefore, practitioners need not be concerned with bioaccumulation of ketoprofen, as they must be with phenylbutazone.

Ketoprofen is approved for use in horses for intravenous administration. The results of a number of studies indicate that the bioavailability of several formulations of the product is very low with both oral and rectal administration.8,9

D. Regulatory Issues
In regard to the pharmacokinetic parameters of ketoprofen, regulatory officials need to be aware that 8 h after administration of a recommended dose, the plasma concentrations of ketoprofen will generally be less than 50 ng/ml.7 Although urinary concentrations of ketoprofen are generally higher than concurrent plasma levels, the limit of detectability for some analytical methods, such as thin-layer and high-performance liquid chromatography, may be exceeded 8–12 h after administration. As ketoprofen has been reported to have effects for 12–24 h, depending on the model and the parameter being measured, this short period of detectability makes regulation of the use of this compound problematic. Analytical laboratories and regulatory veterinarians need to work together to ensure appropriate use of ketoprofen, as well as other NSAID’s with rapid clearance parameters.

3. Conclusions
In the horse, ketoprofen is an effective anti-inflammatory agent with a long duration of effect. This may present advantages to practitioners, as it is recommended to be administered once a day via an intravenous route. Other NSAID’s, such as phenylbutazone and flunixin, however, can be dosed orally, allowing for layman administration. This may or may not be an advantage to practitioners, depending on the clinical setting. Recent findings indicate that most NSAID’s have anti-inflammatory effects beyond the inhibition of cyclo-oxygenase. Therefore, practitioners may find one NSAID more or less effective, depending on the patient and the clinical condition being treated. In refractory cases, trial periods of different NSAID’s may be necessary to determine which agent will be most effective.

Veterinarians concerned with regulating the use of NSAID’s need to be aware of the rapid clearance but prolonged effect of ketoprofen.

References
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