Pharmacokinetics of ketorolac tromethamine in horses after intravenous, intramuscular, and oral single-dose administration

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are an integral component of equine analgesia, yet currently available NSAIDs are both limited in their analgesic efficacy and have adverse effects. The NSAID ketorolac tromethamine (KT) is widely used in humans as a potent morphine-sparing analgesic drug but has not been fully evaluated in horses. The purpose of this study was to determine the pharmacokinetic profile of KT in horses after intravenous (i.v.), intramuscular (i.m.), and oral (p.o.) administration. Nine healthy adult horses received a single 0.5-mg/kg dose of KT via each route of administration. Plasma was collected up to 48 h postadministration and analyzed for KT concentration using HPLC/MS/MS. Noncompartmental analysis of i.v. dosage indicated a mean plasma clearance of 8.4 (mL/min)/kg and an estimated mean volume of distribution at steady-state of 0.77 L/kg. Noncompartmental analysis of i.v., i.m., and p.o. dosages indicated mean residence times of 2.0, 2.6, and 7.1 h, respectively. The drug was rapidly absorbed after i.m. and p.o. administration, and mean bioavailability was 71% and 57% for i.m. and p.o. administration, respectively. Adverse effects were not observed after i.v., i.m., and p.o. administration. More studies are needed to evaluate the analgesic and anti-inflammatory properties of KT in horses.

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INTRODUCTION

Pain management is an active area of investigation in veterinary medicine. Managing pain in equine patients relies primarily on drug intervention, as other aspects of multimodal therapy are often impractical or cost prohibitive. Nonsteroidal anti-inflammatory drugs (NSAIDs) are an integral component of equine pain management as they demonstrate both anti-inflammatory and analgesic effects. The currently available NSAIDs labeled for use in horses are used to treat a wide variety of conditions associated with varying degrees of pain. Despite standard analgesic therapy, horses may still experience moderate to severe pain associated with certain conditions such as acute laminitis or following surgery. In a recent evaluation of 34 horses undergoing exploratory laparotomy, 65% of horses experienced moderate to severe pain following surgery despite ‘standard of care’ analgesic therapy (Graubner et al., 2011). The horses in the Graubner et al.’s study received flunixin meglumine (0.5 mg/kg i.v.) every 8 h and were evaluated for pain using a multidimensional pain scoring system based on physiological and behavioral parameters. In a retrospective study of 300 equine cases of surgical colic, postoperative pain was reported in 32% of horses that received flunixin meglumine (0.25 mg/kg i.v.) every 8 h after recovery from anesthesia. Pain was the most common reason recorded for euthanasia in these horses (Mair & Smith, 2005). Opiate drugs, such as morphine and butorphanol, have been used to provide adjunctive analgesia in horses receiving NSAIDs (Sellon et al., 2004); however, their use is associated with significant side effects in horses including behavior changes and gastrointestinal hypomotility that often limit their use in high-risk patients, regardless of pain score (Kohn & Muir, 1988; Sellon et al., 2004; Boscan et al., 2006).

Ketorolac tromethamine (KT) is a pyrrolizine carboxylic acid derivative NSAID and nonselective cyclooxygenase (COX) inhibitor. While it is widely used in human medicine, primarily as a postoperative analgesic for moderate to severe pain, KT has not been thoroughly evaluated in horses (Rooks et al., 1982; Planborg et al., 1994; Ready et al., 1994; Blackburn et al., 1995; Etches et al., 1995; O’Hara et al., 1997; Ferraresi et al.,

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Ketorolac tromethamine is commonly administered intravenously (i.v.) or as a constant rate infusion (CRI) in humans, even though it is labeled for intramuscular (i.m.) and oral (p.o.) use (Ready et al., 1994; Blackburn et al., 1995; Etches et al., 1995). Numerous studies in human medicine have evaluated KT as a morphine-sparing analgesic in postoperative patients. The results of these studies indicated a 22–44% reduction in morphine consumption when patients were treated with morphine and ketorolac for the first 24 h following abdominal or orthopedic surgery vs. morphine alone (Blackburn et al., 1995; Etches et al., 1995; O’Hara et al., 1997). The adverse effects of KT in humans are similar to those associated with all NSAIDs, including gastrointestinal ulceration and increased risk of bleeding, but the overall incidence of adverse effects in postoperative patients is low (Elia et al., 2005). Ketorolac tromethamine has been shown to be equivalent in safety to the NSAIDs diclofenac and ketoprofen in postoperative human patients (Forrest et al., 2002). In rats, KT has demonstrated an anti-inflammatory potency up to 50 times that of phenylbutazone and antipyretic properties 20 times that of aspirin (Rooks et al., 1982). When administered orally in mice, KT was found to be more than 350 times as potent as phenylbutazone with respect to analgesia (Rooks et al., 1982, 1985). Studies in mice and rats have indicated that the relative analgesic potency of KT is even greater than its anti-inflammatory potency (Rooks et al., 1982, 1985).

We are aware of only two studies that have investigated the pharmacokinetic profile of KT in adult horses. A 1994 study reported pharmacokinetic data after a single 300 mg/kg i.v. or i.m. dose of KT in six adult horses (Planborg et al., 1994), but the study failed to account for individual horse variability as it was not a crossover design. A more recent study evaluated KT in six colts (0.5 mg/kg i.v.) undergoing castration (Ferraresi et al., 2014). The colts in that study received several other medications concurrently and underwent general anesthesia, two factors that have the potential for confounding kinetic data as it is unknown how drug interactions or anesthesia affects metabolism of KT in the horse. The objective of the study reported here was therefore to evaluate the pharmacokinetic profile of KT in healthy adult horses after i.v., i.m., and p.o. single-dose administration and to investigate the potential for adverse effects following KT administration. A single dosage of 0.5 mg/kg was selected for investigation based on extrapolation from recommended human dosage protocols and previous pharmacokinetic studies in the horse and dog (Planborg et al., 1994; Matthews et al., 1996; Pasloske et al., 1999; Cagnardi et al., 2013).

MATERIALS AND METHODS

Animals and experimental design

Nine adult horses from the Purdue University teaching herd were utilized for the crossover pharmacokinetic study. The horses were determined to be healthy on the basis of physical examination, complete blood count (CBC), and serum biochemical analysis (SBA) and had no history of NSAID administration within 2 months prior to the start of the study. A repeated Latin square design was used to ensure that each horse received each route of drug administration (i.v., i.m., p.o.). Horses were randomly assigned a number (1 through 9) and divided into groups of 3, and each trial was staggered over the course of 3 days. The first route of administration was randomly assigned to each horse. The horses consisted of six mares and three geldings that ranged in age from 6 to 24 years, with a mean of 15 ± 6 years. Five breeds were represented, including three Standardbreds, two Thoroughbreds, two Warmbloods, one Saddlebred, and one Quarter Horse. The horses weighed 460–650 kg and were weighed immediately prior to the start of each trial to ensure accurate dosing. All horses gained weight over the course of the study, with a mean weight gain of 21.6 ± 9.6 kg. This was attributed to access to lush forage as the study took place between April and June when the horses were housed on green pasture. All procedures in this study were approved by the Institutional Animal Care and Use Committee at Purdue University.

Drug administration

A 0.5-mg/kg dosage of KT was used for i.v., i.m. (30 mg/mL; Wockhardt USA Inc., Parsippany, NJ, USA), and p.o. (10 mg/tablet; Teva Pharmaceuticals, North Wales, PA, USA) administration, with a 2-week washout period between each trial. The 0.5-mg/kg dose of KT was equivalent to a KT dose of 0.34 mg/kg. Injectable drug doses were rounded up to the nearest 0.1 mL; oral doses were rounded up to the nearest whole tablet. The washout period was selected to exceed the anticipated elimination half-time by at least 10 times. For the first 24 h of each trial, the horses were housed in box stalls with free access to grass hay, alfalfa hay, and water. The horses were not fasted before or after p.o. administration to mimic clinical administration. After the first 24 h of each trial and during the washout period, the horses were housed on pasture.

Intravenous jugular catheters were aseptically placed the night before the start of each trial; horses undergoing i.v. drug administration had a catheter placed in each jugular vein. The catheter used to deliver the KT was removed after drug administration; the contralateral catheter was used for all blood collections. Intramuscular injection of KT was performed in the neck muscle opposite that of the jugular catheter. The oral dose of KT was delivered via nasogastric tube; the tablets were first dissolved in 60 mL of water, added to the nasogastric tube, and then followed by 3 L of water to ensure complete delivery of the drug.

Heparinized blood samples were collected from the jugular vein catheter immediately prior to drug administration (t = 0) and at 5, 10, 15, 20, 30, 45, 60, and 90 min and 2, 3, 4, 6, 8, 10, 12, 24, and 48 h after drug administration. Plasma was harvested by centrifugation at 1300 g for 5 min within 6 h of collection and stored at −80 °C until analyzed. Ketorolac tromethamine is stable in plasma for at least 30 days when
stored at −20 °C (Mroszczak et al., 1987) or −80 °C (Raju et al., 2012).

Adverse effects
Horses were continually monitored during the first 12 h of each trial, and complete physical examinations were performed at \( t = 0, 4, 12, 24, \) and 48 h. A CBC (Abbott Cell-Dyn 3500 Hematology Analyzer, Abbott Park, IL, USA) and SBA (Johnson & Johnson Vitros 5,1 FS Chemistry Analyzer, Holliston, MA, USA) were performed at \( t = 0 \) and \( t = 24 \) h. Subjective assessments were made regarding changes in behavior, appetite, and fecal consistency, as well as evidence of inflammation at the i.m. injection site (characterized by the presence of heat, swelling, or pain).

Sample analysis
Sample preparation. Plasma samples were prepared as described prior to high-performance liquid chromatography (HPLC) tandem mass spectrometry (MS-MS) analysis (Radwan et al., 2010; Raju et al., 2012). Briefly, an internal standard (IS) solution containing 50 \( \mu \)L etodolac (500 ng/mL in 50% water:50% acetonitrile) was added to 200 \( \mu \)L plasma and vortexed (Patrick et al., 2011). Protein precipitation was performed by adding 800 \( \mu \)L of a solution of 0.1% formic acid in acetonitrile. The mixture was vortexed and then centrifuged at 12 000 \( g \) for 5 min. Aliquots of 500 \( \mu \)L were transferred to HPLC vials with 10 \( \mu \)L submitted for HPLC/MS-MS analysis.

HPLC/MS-MS analysis. Ketorolac tromethamine plasma levels were quantitated by HPLC/MS-MS. Separation was performed on an Agilent Rapid Res 1200 HPLC system using an Agilent Zorbax XDB-C18 (2.1 \times 50 mm, 3.5 \( \mu \)m) column (Agilent ZORBAX Eclipse XDB column: Agilent Technologies, Santa Clara, CA, USA). Mobile phase A was \( \text{H}_2\text{O} \) with 0.1% formic acid, and mobile phase B was acetonitrile (ACN) with 0.1% formic acid. A linear gradient elution was used as follows: initial conditions 35% B; 0–8 min: gradient to 70% B; 8–8.5 min: gradient to 90% B; and 8.5–9.5 min: gradient held 90% B. During compound elution, a flow rate of 0.4 mL/min was used. Column re-equilibration was 9.5–10.5 min: gradient to 35% B and 10.5–13.5 min: gradient held 35% B. During re-equilibration, flow rate was increased to 0.6 mL/min and column flow was diverted to waste. Retention time for KT was 3.2 min and for etodolac was 6.9 min.

Analytes were quantified using MS/MS utilizing an Agilent 6460 triple quadrupole mass spectrometer with electrospray ionization (ESI) (Agilent 6460 Triple Quadrupole mass spectrometer; Agilent Technologies). Quantitation was based on multiple reaction monitoring (MRM). For KT, ESI-positive mode was used with a transition of 256.1–104.9 and a collision energy (CE) of 18 V. For etodolac, ESI-negative mode was used with a transition of 286.1–212.1 and a CE of 20 V. Both compounds used a fragmentor energy of 125 V and a dwell time of 300 ms. Source parameters were as follows: nitrogen gas temperature = 350 °C and flow rate = 9 L/min, nebulizer pressure = 40 psi, sheath gas temperature = 250 °C, sheath gas flow rate = 7 L/min, and capillary potential = 3500 V. All data were collected and analyzed with Agilent MassHunter B.03 software. Quantitation was based on a 6-point standard curve, with KT concentrations ranging from 2.5 to 5000 ng/mL using a diluent of acetonitrile and water (1:1, v/v). Standard curves were fit to a quadratic function, with a 1/x curve fit weighting. Correlation coefficients >0.9997 were obtained. Curves were used if the standard concentration accuracy for each point was between 95% and 105%. Responses for KT were normalized against the internal standard (RR = response ratio).

The limit of quantitation was 1.2 ng/mL and the limit of detection was 0.5 ng/mL, as defined as a signal-to-noise (SNR) ratio of 10:1 and 3:1, respectively, determined using authentic standards. Matrix effects and extraction recoveries were assessed using the approach detailed by Trufelli et al. (2011). Matrix effects were determined by ratioing the RR in matrix-matched standards to the RR in neat standards. The matrix effect was determined at 2.5 (low), 250 (middle), and 5000 (high) ng/mL, which were 122%, 127%, and 99.2%, respectively (n = 6). Extraction efficiencies were determined by ratioing the RR in preextraction spiked plasma to matrix-matched standards. The extraction efficiencies were determined at 2.5 (low), 250 (middle), and 5000 (high) ng/mL, which were 84.3%, 89.0%, and 123%, respectively (n = 6). As no significant matrix effects or extraction efficiencies were observed, calibrants and control samples were prepared using a solvent of acetonitrile and water (1:1, v/v). At 2.5 (low), 250 (middle), and 5000 (high) ng/mL, the precision (relative standard deviation (RSD)) of the standard curves was 7.0%, 3.7%, and 1.7%, respectively (n = 6). Based on a 100 ng/mL control sample, the intraday assay precision RSD ranged from 3.6% to 13.1%, and the interday precision (n = 7) was 8.3%. The intraday accuracy RSD ranged from 95.8% to 103.9%, and the interday accuracy (n = 7) was 98.8%.

Pharmacokinetic analysis
Pharmacokinetics were characterized using standard compartmental and noncompartmental methods and a software program (PKSolver, doi:10.1016/j.cmpb.2010.01.007). A variety of weighting schemes were examined, and the best model fit (inverse of concentration squared) was determined using Akaike’s information criterion and the smallest sum of squared residuals.

Compartmental pharmacokinetic variables were attempted to be obtained for i.v., i.m., and p.o. data from each horse by fitting the plasma KT concentration–time data to a two- and three-compartment open model using various weighting schemes. Compartment models could not be satisfactorily fit to i.v. data for the majority of horses and to i.m. and p.o. data for any horse. Noncompartmental analysis for i.v., i.m., and p.o. data from each horse was fit using the last three or more data points from the semilog plasma concentration–time curve to

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calculate the elimination rate constant (\(\dot{z}_Z\), slope of the terminal linear phase). The area under the curve (AUC\(_{ao}\)) and the area under the first moment curve (AUMC\(_{ao}\)) were calculated for each horse and treatment from the KT concentration–time relationship using the trapezoidal method, with the area from the last time point extrapolated to infinity using the last measured plasma KT concentration and \(\dot{z}_Z\). The elimination half-life was calculated as 0.693/\(\dot{z}_Z\). Mean residence time (MRT) was calculated from the ratio of AUMC\(_{ao}\) to AUC\(_{ao}\). Total plasma clearance (Cl\(_{p}\)) was calculated as dose/AUC\(_{ao}\). The apparent steady-state volume of distribution (\(V_{\text{d(ss)}}\)) was calculated as dose \times AUMC\(_{ao}\)/AUC\(_{ao}\)^2. Mean absorption time (MAT) for i.m. or p.o. administration was calculated as MAT\(_{IM} = \text{MRT}_{IM} - \text{MRT}_{IV}\) or MAT\(_{PO} = \text{MRT}_{IV}\). Bioavailability was determined by dividing the i.m. or p.o. AUC\(_{ao}\) by the i.v. AUC\(_{ao}\) and multiplying by 100.

Statistical analysis

Significance was set at \(P < 0.05\). Data were expressed as mean ± SD, and plasma concentration–time data was presented in a semi-logarithmic graph. A mixed model analysis of variance (ANOVA) with repeated measures was used to evaluate the CBC and SBA data in order to account for the crossover experimental design (SAS 9.3, SAS Inc, Cary, NC, USA).

RESULTS

Pharmacokinetics

The plasma concentration–time relationship of KT following a single 0.5-mg/kg i.v. dose is depicted in Fig. 1, and relevant pharmacokinetic variables are summarized in Table 1. Plasma KT concentration was below the limit of detection for all horses and routes of administration at 48 h. Mean total plasma clearance (Cl\(_{p}\)) was rapid at 8.4 (mL/min)/kg, and the estimated mean volume of distribution at steady-state (\(V_{\text{d(ss)}}\)) was 0.77 L/kg.

![Semi-logarithmic graph of plasma ketorolac tromethamine concentration (mean ± SD) vs. time after intravenous, intramuscular, and oral administration of ketorolac tromethamine (0.5 mg/kg) to healthy horses (n = 9).](https://example.com/fig1.png)

The plasma concentration–time relationship of KT following 0.5-mg/kg i.m. or p.o. dosing is depicted in Fig. 1, and relevant pharmacokinetic variables are summarized in Table 1. The mean observed time to maximum concentration (\(t_{\text{max}}\)) after i.m. or p.o. administration was 25 and 19 min, respectively, indicating rapid absorption. The observed peak mean plasma concentrations (\(C_{\text{max}}\)) after i.m. or p.o. administration were 0.58 and 0.31 μg/mL, respectively. The MRT was 2.0 h for i.v., 2.6 h for i.m., and 7.1 h for p.o. administration. Calculated mean bioavailability (F) of KT after i.m. and p.o. delivery was 71% and 57%, respectively.

Adverse effects

There were no significant changes in the physical examination or CBC of any horse during any trial period (Table 2). No subjective changes were noted in the behavior, appetite, or fecal consistency of any horse during any trial period. While none of the i.m. injection sites showed any clinical evidence of pain or inflammation, plasma creatinine kinase activity was increased at 24 h after i.m. injection (\(P = 0.012\)). The mean CK value preinjection was 136 ± 34 IU/L vs. a postinjection CK value of 162 ± 50 IU/L (Table 2).

DISCUSSION

Similar to other species, the pharmacokinetic profile of KT after i.v. administration was characterized by a low volume of distribution and rapid clearance from the plasma compartment (Santos et al., 2001; Nagilla et al., 2009). The drug was rapidly absorbed after i.m. and p.o. administration, and no adverse effects were observed after single-dose administration.

Mean total plasma clearance of KT was higher in the current study (8.4 mL/min/kg) than previously reported for horses by Planborg et al. (1994) (2.8 mL/min/kg) and Ferraresi et al. (2014) (5.6 mL/min/kg). Differences in drug clearance after i.v. administration of a water-soluble drug such as KT are primarily due to species differences in the rate of hepatic KT metabolism or renal blood flow, as KT is primarily metabolized by the liver to form glucuronide conjugates and excreted by the kidneys (Mroszczak et al., 1987). Species differences in urine pH may impact plasma clearance of acidic drugs such as KT, as alkaline urine has the potential to ion trap KT and thereby prevent reabsorption; however, this is considered an unlikely reason for the high clearance in horses, as KT has a pKa value of 3.5, which indicates effectively full dissociation even in acidic urine (pH = 5.5). Moreover, clearance of KT after i.v. administration is variable in ruminants that typically have an alkaline urine, being 12.4 (mL/min)/kg in adult sheep (Santos et al., 2001) and 8.8 (mL/min)/kg in adult goats (Nagilla et al., 2009), but only 0.8 (mL/min)/kg in calves (Nagilla et al., 2007). Differences in drug clearance may also be due to differences in plasma protein binding between species, as small changes in binding percentage for highly bound drugs such as KT can have a large impact on drug
availability for hepatic metabolism or urinary excretion (Nagilla et al., 2007). Additional studies to determine the rate of hepatic metabolism are indicated to confirm the supposition that rapid hepatic metabolism is the reason for the high plasma clearance of KT in horses.

It is not clear why Planborg et al. (1994) found KT to have a much slower clearance than that reported in our study, but only 3 horses were used in that study to estimate clearance, and their assay was able to detect KT only up to 3 h post administration, which was probably too short a time interval to provide an accurate estimate of clearance. The colts in the Ferraresi et al. study received acepromazine, detomidine, ketamine, and diazepam in addition to KT before undergoing general anesthesia with isoflurane; clearance of KT is expected to be decreased in horses receiving these drugs because of drug-induced decreases in cardiac output, mean arterial pressure, renal blood flow, and core body temperature (Gelman, 1976; Gelman et al., 1984; Wood & Wood, 1984). Given the rapid clearance of KT in the horse, the most useful application of the drug in horses is likely to be as a short-term i.v. CRI or oral administration in horses with normal gastrointestinal motility. While there are no reports in the veterinary literature, CRI of NSAIDs has been described in human medicine for treatment of fever or pain due to surgery or cancer (Beattie et al., 1997; Moselli et al., 2010; Grimsby et al., 2012). When administered as a CRI in humans, KT has been shown to be safe and effective at providing analgesia and reducing the use of opiates (Burns et al., 1991; Myers & Trotman, 1994).

The mean $V_{diss}$ of KT in the current study (0.77 L/kg; median 0.49 L/kg) was similar to that for other NSAIDs (Mroszczak et al., 1987) and was most likely due to a moderately high degree of plasma protein binding. While not specifically
evaluated in the current study, Ferraresi et al. (2014) reported a plasma binding of 76% in horse plasma. Plasma binding of KT is 72.0% in mice (Mroszczak et al., 1987), 92.1% in rats (Mroszczak et al., 1987), 98.9% in dogs (Cagnardi et al., 2013), and 99.2% in humans (Mroszczak et al., 1987).

The mean plasma elimination half-life of KT in this study was 8.7 h (median 5.8 h). For comparison, sheep have a much shorter elimination half-life (18 min) after i.v. administration (Santos et al., 2001), whereas studies in dogs (Pasloske et al., 1999), calves (Nagilla et al., 2007, 2009), and the 1994 study in horses (Planborg et al., 1994) reported an elimination half-life similar to that observed in humans of approximately 4–6 h.

The pharmacokinetic profile of KT after i.m. injection could not be adequately characterized using a compartmental model; consequently, noncompartmental analysis was performed. Ketorolac tromethamine was rapidly absorbed after i.m. injection in horses, with a mean absorption time of 36 min (95% confidence interval for mean absorption time of 5.5–6.7 h) that was similar to that reported in sheep (11 min) (Santos et al., 2001) and humans (46 min) (Jung et al., 1988).

Oral administration of KT resulted in a $t_{\text{max}}$ of 19 min in horses, which is shorter than the $t_{\text{max}}$ in dogs (51 min (Pasloske et al., 1999) and humans (53 min (Jung et al., 1988)). While the oral pharmacokinetics of KT have been evaluated in goats and calves, it is difficult to compare oral drug administration in ruminants vs. nonruminant animals given the vast difference in drug absorption resulting in a delayed $t_{\text{max}}$ of 6.5 h in calves and 8.9 h in goats (Nagilla et al., 2007, 2009). The differences in $t_{\text{max}}$ between horses and dogs may be related to method of administration: the tablets in the current study were dissolved in 60 mL of water prior to administration and then followed by 3 L of water, which may have facilitated gastric emptying and therefore a faster rate of delivery to the small intestine. The oral formulation given to dogs was reported to be a capsule, which may have delayed drug absorption to the small intestine. The oral formulation given to dogs was reported to be a capsule, which may have delayed drug absorption to the small intestine.
erate oral bioavailability of KT found in this study, and all other studies in a variety of species (Mroszczak et al., 1987; Pasloske et al., 1999; Nagilla et al., 2007), it is unlikely that buccal absorption would have had an impact on the plasma KT concentration–time profile. Per os administration of drugs is not usually accompanied by water, and delivery likely results in partial loss of drug. Thus, intragastric administration of KT may have falsely increased oral bioavailability in this study. Interestingly, the plasma concentration–time relationship after oral KT administration appeared to be biphasic, with a slightly higher plasma KT concentration present than anticipated from approximately 4–12 h after administration. A more exaggerated pattern has been observed in dogs administered KT intravenously (Cagnardi et al., 2013), leading to speculation that enterohepatic cycling of KT may have been present.

As reported in humans and other species (Mroszczak et al., 1987; Jung et al., 1988; Pasloske et al., 1999; Nagilla et al., 2007, 2009), the mean bioavailability of KT after both i.m. and p.o. administration was moderate at 71% and 57%, respectively. This is similar to the i.m. bioavailability previously reported in horses (69%) (Planborg et al., 1994).

While the target plasma concentration of KT for effective analgesia in horses is not known, an EC50 of 0.37 μg/mL for plasma KT concentration has been calculated for humans using pharmacodynamic modeling (Mandema & Stanski, 1996). Interestingly, oral administration of KT failed to achieve a mean plasma KT concentration of 0.37 μg/mL and i.m. administration resulted in plasma KT concentration exceeding 0.37 μg/mL for <1 h.

Despite the extensive literature on analgesic properties of KT in humans, veterinary studies are sparse. Only one analgesic trial has been performed in horses, when six colts undergoing elective castration received KT preoperatively (0.5 mg/kg i.v.) (Ferraresi et al., 2014). All colts experienced adequate analgesia, as determined by a visual analog score, although there was no untreated control group and investigators were therefore not masked to treatment (Ferraresi et al., 2014). Several studies have evaluated the clinical efficacy of KT in providing postoperative analgesia in dogs. In a randomized controlled trial, KT given at a dose of 0.5 mg/kg i.m. was as effective as flunixin meglumine (1.0 mg/kg i.m.) and superior to both butorphanol (0.4 mg/kg i.m.) and oxymorphone (0.05 mg/kg i.m.) in providing consistent postoperative analgesia (Mathews et al., 1996). Similar findings were observed in a clinical trial during which 15 dogs received KT (0.5 mg/kg i.v.) for analgesia associated with elective castration, although no control group was used in that study (Cagnardi et al., 2013). Given the diversity of individual pain sensitivity and the variety of painful medical conditions, determining the effective therapeutic concentration of a drug is difficult, even when patients can verbally communicate their pain level. Furthermore, the target therapeutic concentration of a drug is likely to vary among species. Therefore, the appropriate dosage of a drug must be based on attaining the plasma concentration that has been shown to be both effective and safe.

While no adverse effects were noted in the current study, NSAID use in all species is associated with damage to the renal medulla and gastrointestinal mucosa due to inhibition of prostaglandin E2 and vasoconstriction. The safety of KT has been evaluated extensively in humans with mixed results. While several studies report that the risk of adverse effects is not higher than other NSAIDs (Forrest et al., 2002; Elia et al., 2005), other studies have cited KT having a higher relative risk of upper gastrointestinal bleeding in comparison with other human NSAIDs (Castellague et al., 2012). The risk of adverse effects in humans has been shown to be increased in certain patients with preexisting conditions such as renal or gastrointestinal disease, coagulopathy, or those receiving concurrent administration of other NSAIDs. Given these potential risks in the human population, use of KT in the United States is restricted to no more than 5 days of treatment (Reinhart, 2000). While no adverse effects have been noted in any of the previous veterinary single-dose pharmacokinetic studies, only one study has specifically evaluated the safety of multiple doses of KT. In this study, no difference in adverse effects was found between KT and flunixin meglumine in dogs after three doses of either drug administered 6 h apart (Mathews et al., 1996). Given the potentially severe adverse effects of NSAIDs in horses, the safety of KT must be evaluated further.

The increase in CK values noted after i.m. injection may or may not be clinically relevant. Creatine kinase is a sensitive indicator of muscle damage; a small amount of muscle damage can result in a detectable elevation in CK and does not necessarily result in clinically detectable pain or inflammation (Leffvre et al., 1996). None of the horses experienced clinical evidence of injection site reaction in this study or had a CK value that was outside of the reference range; however, the postinjection samples were collected 24 h after injection and CK activity peaks 6–12 h after muscle injury (Anderson, 1975). While the KT administered to horses in this study was formulated for i.m. use in humans and is commonly used without significant adverse effects, the potential for muscle damage may become apparent with repeated or prolonged dosing in horses.

In conclusion, the pharmacokinetic profile indicates rapid absorption when KT is administered orally or by i.m. injection in healthy adult horses with no obvious adverse effects after a single 0.5-mg/kg dosage. Further studies are necessary to evaluate the analgesic and anti-inflammatory properties of a CRI of KT in the horse, as well as the drug’s safety profile when administered as a CRI.

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REFERENCES


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