30-Day Oral Acetaminophen Tolerance in Adult Horses

Sarah E. Foreman
Augustana College, Rock Island Illinois

30-Day Oral Acetaminophen Tolerance in Adult Horses

Sarah Foreman

Abstract

There are no controlled studies of acetaminophen toxicity in horses. The objective was to test the hypotheses that oral acetaminophen administered at a dosage 25% higher than that sometimes used in horses would result in measurable hepatic toxicity as seen in humans and other species. Six healthy adult horses were administered 25 mg/kg acetaminophen powder in corn syrup twice daily for 30 days. Three other horses served as negative controls receiving only corn syrup. Jugular venous blood samples were obtained on days 7 and 1 before treatment; on treatment days 1, 2, 5, 8, 12, 15, 19, 22, 26 and 30; and on days 3 and 7 after treatment ceased.

Samples were analyzed the same day for complete blood counts and plasma biochemistry concentrations including hepatic and renal indices. Repeated measures analysis of variance and *post hoc* Tukey's test were used to identify differences between treatment groups at a significance level of P<0.05. On all sampling days, there were no differences between treated and untreated horses (P>0.05), and all measured values were within the normal range for this laboratory.

It was concluded that acetaminophen at this oral dosage was not toxic in any measurable manner to the 6 horses receiving the drug in this way. It is postulated that the use of twice daily 20 mg/kg orally should be safe for periods less than 30 days in healthy horses.

Introduction

The use of acetaminophen (paracetamol outside the USA) has remained rare in equine practice. West et al. (2011) reported the use of acetaminophen in a badly foundered obese Welsh gelding which had become poorly-responsive to conventional non-steroidal anti-inflammatory drugs (NSAIDs). Foreman et al. (2016) showed acetaminophen efficacy in a reversible model of equine foot lameness. However, there remain no refereed blinded controlled documentations of acetaminophen toxicity in horses. The objective was to test the hypothesis that oral acetaminophen administered at a dosage 25% higher than that sometimes used clinically in horses would result in measurable hepatic toxicity as seen in humans and other species.

Materials and Methods

All materials and methods used for this study were performed under the approval and authority of the University of Illinois Institutional Animal Care and Use Committee (Protocol #17107).

Subjects: Nine healthy adult horses (3 WB, 3 STB or STB-X, 1 TB, 1 QH, 1 Arabian; age mean 14.4±4.4, median 14, range 5-21 years; 2 geldings, 7 mares; mean wt 509±114 kg) were assigned randomly to negative control (n=3) or acetaminophen-treatment (n=6) groups. Complete physical, hematological, serum biochemical, and lameness examinations were performed to ensure that each subject was normal before drug was administered. Subjects were negative for equine infectious anemia using agar gel immunodiffusion. A minimum of 7 days of stall rest acclimatization were allowed after admission and before any trials were begun.

Six horses were administered generic acetaminophen (Wal-Mart brand "Equate" caplets or tablets) orally in a paste at a dosage of 25 mg/kg twice daily for 30 days. Horses were weighed twice weekly and daily drug doses were adjusted to changes in body weight the day following new weights. As negative controls, 3 horses received no medication but received the same syrup used to make the acetaminophen paste orally twice daily.

Blood samples were analyzed the same day for complete blood counts and plasma biochemistry concentrations including hepatic and renal indices. Repeated measures analysis of variance and *post hoc* Tukey's test were used to identify differences between treatment groups at a significance level of P<0.05.

Results

At no time before, during, or after acetaminophen administration did these horses have elevations of liver or renal indices, nor did the initial indices change throughout the experiment. There was no apparent effect of acetaminophen administration on horses compared to the negative controls. Selected blood indices are graphed in figures 1-3.

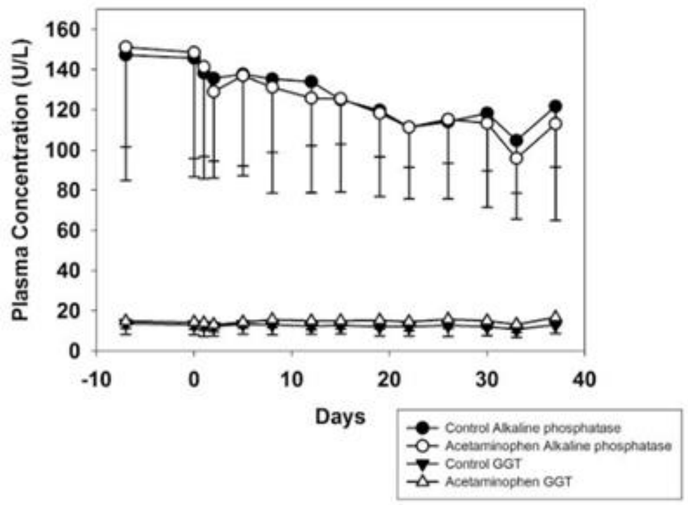

Figure 1. Mean (±S.D.) plasma gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) concentrations in negative control and acetaminophen-treated horses on 7 and 1 days before treatment; on treatment days 1, 2, 5, 8, 12, 15, 19, 22, 26 and 30; and 3 and 7 days after treatment ceased. There were no differences between treated and untreated horses (P>0.05), and all values were within the normal range for this laboratory.

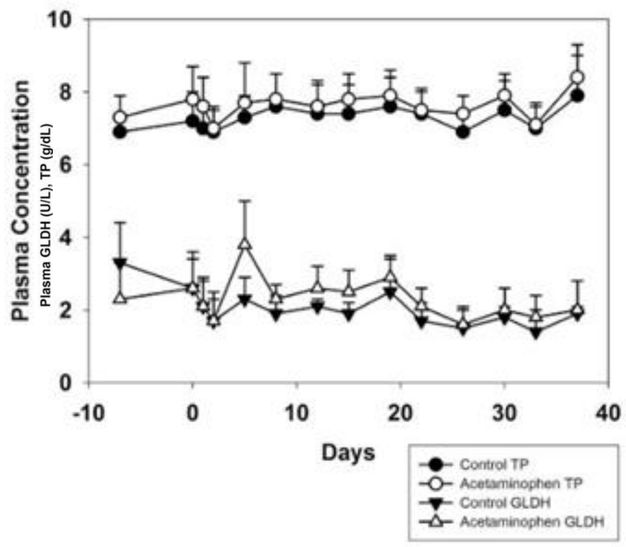

Figure 2. Mean (±S.D.) plasma gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) concentrations in negative control and acetaminophen-treated horses on 7 and 1 days before treatment; on treatment days 1, 2, 5, 8, 12, 15, 19, 22, 26 and 30; and 3 and 7 days after treatment ceased. There were no differences between treated and untreated horses (P>0.05), and all values were within the normal range for this laboratory.

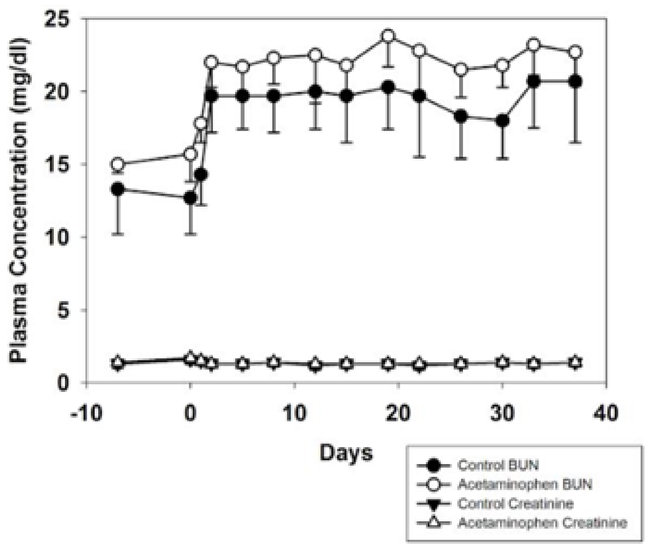

Figure 3. Mean (±S.D.) plasma blood urea nitrogen (BUN) and creatinine concentrations in negative control and acetaminophen-treated horses on 7 and 1 days before treatment; on treatment days 1, 2, 5, 8, 12, 15, 19, 22, 26 and 30; and 3 and 7 days after treatment ceased. There were no differences between treated and untreated horses (P>0.05), and all values were within the normal range for this laboratory.

Discussion

The analgesic effects of acetaminophen (*N*-acetyl-*p*-aminophenol) are thought to be mediated via serotonin and cannabinoid pathways. Acetaminophen is well-absorbed (91%) from the small intestine in horses but more poorly in dogs (45%) (Neirinckx et al. 2010). It is metabolized via hepatic glucuronidation in horses but there are no pharmacodynamic data and, until now, no toxicity data in horses. The more commonly-used non-steroidal anti-inflammatory drugs (NSAIDs) work by inhibiting one or both of the isoenzymes of cyclooxygenase (COX), but pan-COX inhibitors often result in horses in gastric and colonic ulcers and renal disease. If acetaminophen can be shown to be safe and efficacious in horses, it might provide an alternative to conventional NSAIDs for horses suffering from NSAID-toxicity or requiring adjunctive pain relief.

GLDH, AST, Alkaline phosphatase, and GGT are all hepatocellular or biliary-specific enzymes which are used as determinants of hepatic health in horses. Because all these variables remained normal throughout treatment and for 7 days afterward, acetaminophen at this dosage twice daily seems to be safe in horses for a prolonged period of time. BUN and creatinine are indicators of renal disease or toxicity, and were monitored because clients and veterinarians often ask if acetaminophen has any renal toxicity; they are so used to NSAID-induced renal disease that they expect it with acetaminophen as well. However, we saw no evidence of renal effects of acetaminophen in these horses. Plasma total protein is a simple indicator of hydration status and was unchanged in this experiment.

FDA-approved New Application for Drug Approval (NADA) studies require considerably more horses for safety and tolerance studies, and require euthanasia and necropsy of those horses after chronic drug administration. For example, the NADA for FDA approval of an equine dose and label indication for ceftiofur sodium (https://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/UCM539438.pdf) required the use of considerably more horses, and required in some experiments the termination and necropsy of those horses. In that series of experiments, Dr. Jonathan Foreman participated in clinical trials studying ceftiofur efficacy against both negative and positive controls (Federal Drug Administration 1994). It was not our intent in this current research to pursue a NADA-type study. There will never be enough money in the marketplace to justify the high cost of doing an NADA study for such an affordable, widely-available generic drug. We simply sought data to justify its safety, or non-safety, for chronic use in horses with chronic musculoskeletal pain, at a very affordable price.

Horses remained in VTH LAC Ward 3 stalls throughout the study to control timing, type, and amount of hay and grain administered twice daily. Grazing would have caused an unquantifiable amount of forage to be eaten by individual horses. Recent work with other drugs in horses (UIUC IACUC #s 14261 and 16055) has documented the effects of feeding on oral drug bioavailability in horses. Dr. Foreman has housed horses in these same stalls for over 90 consecutive days when horses were wearing special shoes which can be damaged by pasture turnout exercise, with no adverse effects to the horses from being housed inside during that period of time. No adverse effects due to chronic housing were observed in these horses; one horse had a stereotypical circling behavior which she had had prior to admission to this study.

Conclusions

It was concluded that this dose, 25% higher than that commonly used in horses with clinical lameness, did not cause renal, hepatic, or red blood cell injury to the horses studied in this experiment. The slightly lower dosage (20 mg/kg twice daily) used more commonly should be safe for most healthy horses for up to 30 days.

References

Federal Drug Administration. Freedom of Information Summary for Supplemental Approval for New Application for Drug Approval 140-338. 1994 Jul 13.

Foreman J, Foreman C, Bergstrom B. Acetaminophen/paracetamol efficacy in a reversible model of equine foot pain. Proc 62nd Annl Conv Am Association Equine Pract 2016: 295-296.

Neirinckx, E., Vervaet, C., de Boever, S. (2010) Species comparison of oral bioavailability, first-pass metabolism and pharmacokinetics of acetaminophen. *Res Vet Sci* 89, 113-119.

West, E., Bardell, D., Morgan, R., Senior, M. (2011) Use of acetaminophen (paracetamol) as a short-term adjunctive analgesic in a laminitic pony. *Vet Anaesthesia and Analgesia* 38, 521-522.