30-Day Oral Acetaminophen Tolerance in Adult Horses

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30-Day Oral Acetaminophen Tolerance in Adult Horses

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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.

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 administered in 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 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 celecoxib sodium (https://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FDADrugGums/FDAdrugGumsmv/CVM09938.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 celecoxib 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 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 UAC Ward 3 stalls throughout the study to control timing, tippe, and amount of hay and grain administered twice daily. Grazing would have caused an unquantifiable amount of forage to be eaten by the individual horses. Recent work with other drugs in horses (UAC, IUC, #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.

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.

![Image](https://via.placeholder.com/150)

Figure 1. Mean (±SD) 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.

![Image](https://via.placeholder.com/150)

Figure 2. Mean (±SD) 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. These were no differences between treated and untreated horses (P>0.05), and all values were within the normal range for this laboratory.

![Image](https://via.placeholder.com/150)

Figure 3. Mean (±SD) 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 (31%) from the small intestine in horses but more poorly in dogs (45%) (Neirinckx et al. 2010). It is metabolized via hepatic glutathione 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 may be a safe alternative to conventional NSAIDs for horses suffering from NSAID toxicity or requiring adjunctive pain relief.

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


