Short-term administration of flunixin meglumine or firocoxib does not alter viscoelastic coagulation profiles in healthy horses

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OBJECTIVE
To evaluate the effect of the cyclooxygenase-2–selective NSAID firocoxib, compared to the nonselective NSAID flunixin meglumine on viscoelastic coagulation parameters in healthy horses.

ANIMALS
12 healthy adult mixed-breed horses.

PROCEDURES
Following a crossover protocol, horses were administered flunixin meglumine (1.1 mg/kg, IV, q 12 h for 5 days), allowed a 6-month washout period, and then administered firocoxib (0.3 mg/kg, PO, once, then 0.1 mg/kg, PO, q 24 h for 4 days). Omeprazole (1 mg/kg, PO, q 24 h) was administered concurrently with each NSAID. Viscoelastic coagulation profiles and traditional coagulation parameters (prothrombin time, partial thromboplastin time, and fibrinogen) were measured before and after each treatment.

RESULTS
Viscoelastic coagulation parameters were within reference intervals before and after both treatments. There was a statistically significant difference between treatments for amplitude at 10 minutes after clot time ($P = .02$) and maximum clot formation ($P = .02$); however, the magnitude of change was not clinically significant.

CLINICAL RELEVANCE
Short-term administration of flunixin meglumine and firocoxib did not result in significant alteration of viscoelastic coagulation profiles in healthy horses. However, clinicians should be aware of possible coagulopathy secondary to NSAID administration with long-term use or critical illness, and further study is indicated.

NSAIDs are commonly used in equine practice to treat pain, inflammation, and fever. Effects of NSAIDs are mediated by inhibition of the cyclooxygenase (COX) cascade, which consists of 2 isoforms, COX-1 and COX-2. NSAIDs have differential selectivity for COX-1 or COX-2, depending on the drug, dose, route, and timing of administration. Preferential inhibition of the induced isoform, COX-2, is thought to maintain anti-inflammatory properties while mitigating detrimental inhibition of COX-1. Firocoxib (Equioxx), the COX-2–selective NSAID licensed for use in equids in the US, has a high COX-2:COX-1 selectivity ratio in horses compared to less selective NSAIDS such as phenylbutazone and flunixin meglumine. While COX-2–selective NSAIDs (coxibs) have been regarded as safer than nonselective NSAIDs, multiple homeostatic functions of COX-2 have been identified that may cause additional undesirable effects when inhibited. Beyond mediating pain and inflammation, the COX isoenzymes play an important role in coagulation homeostasis. COX-1 has procoagulant effects through production of thromboxane, which promotes vasoconstriction and platelet aggregation. COX-2 exerts anticoagulant effects through the synthesis of prostacyclin, which causes vasodilation and prevents platelet aggregation. Selective inhibition of COX-2 may disrupt the homeostatic balance between pro- and anticoagulant effects of COX-1 and COX-2. Thrombotic events have been associated with coxib administration in humans, and adverse cardiovascular events such as heart attack and stroke have resulted in withdrawal of 2 human coxibs from the market.

While thromboembolic diseases like myocardial infarction and stroke are not commonly encountered in horses, the presence of coagulopathy in critically ill horses is well documented. Clinical consequential-
es of coagulopathy in horses include disseminated intravascular coagulation, jugular thrombophlebitis, and laminitis, which all contribute to multiple organ dysfunction, morbidity, and mortality. Clinical trials comparing COX-2–selective and nonselective NSAIDs in critically ill equine patients have not reported significant differences in the incidence of jugular thrombosis. However, these trials have not directly assessed coagulation parameters, and it remains possible that COX-2–selective NSAIDs induce subclinical hypercoagulability in horses. Considering the documented thrombotic events with coxib use in humans, and as COX-2–selective NSAIDs become increasingly popular for use in critically ill horses, it is important to investigate whether these medications alter coagulation homeostasis in horses.

The aim of this study was to evaluate the effect of the COX-2–selective NSAID firocoxib, compared to the nonselective NSAID flunixin meglumine on viscoelastic coagulation parameters in healthy horses. Our null hypothesis was that neither NSAID would result in a significant alteration of viscoelastic coagulation profiles in healthy horses.

Materials and Methods

Study design

Clinically healthy adult horses from the Veterinary Teaching Hospital herd were enrolled in a prospective crossover study. A priori power analysis was performed (95% confidence interval, 80% power), using a 2-sample t test accounting for paired samples, to detect a clinically relevant change in viscoelastic coagulation parameters (the magnitude of relevant change is specific to each parameter, based on 10% or greater deviation from standard normal reference values). Baseline means and SD were chosen from clinical data generated in our hospital, and the parameter with the most variable values between individuals was chosen, resulting in a sample size of 12 horses. All procedures were approved and performed with the oversight of the institutional animal care and use committee.

During treatment, horses were housed in individual stalls with timothy grass/alfalfa mixed hay fed twice daily and water available at all times. Horses were considered clinically healthy on the basis of complete physical examination, serum chemistry profile, and CBC. During each treatment week, horses were monitored with physical exams daily and at examination parameters remained within normal limits, and there was no change in attitude, appetite, or manure production throughout the duration of the study.

Hematologic monitoring

Blood was collected prior to the start of each protocol and following the last dose of NSAID (12 hours after final dose of flunixin meglumine and 24 hours after final dose of firocoxib) for coagulation testing as well as markers of hydration and renal function. For coagulation testing, whole blood samples were obtained by direct venipuncture of a jugular vein using an 18-gauge needle and 3-mL syringe for coagulation testing using a point-of-care viscoelastic coagulation monitor (VCM Vet; Entegris Inc). Briefly, blood was placed in prewarmed test cartridges within 4 minutes of collection and loaded in the VCM Vet device. The viscoelastic coagulation profile included clot time (CT), clot formation time (CFT), angle, maximum clot formation (MCF), amplitude at 10 and 20 minutes after clot time (A10 and A20), and lysis index at 30 and 45 minutes after clot time. Remaining blood was processed in sodium citrate tubes, and sodium citrate anticoagulated plasma samples were stored at –20°C for traditional coagulation profile analysis (prothrombin time [PT], partial thromboplastin time [PTT], and fibrinogen).

Results

Horses

All horses completed the study without complications. The study population consisted of 9 mares, 2 geldings, and 1 stallion with ages ranging from 6 to 22 years (median, 14.5 years). A variety of breeds were represented, including 3 Arabian horses, 2 Standardbreds, 2 Thoroughbreds, 2 Quarter Horses, an Appaloosa, a Missouri Fox Trotter, and a Tennessee Walker. Physical examination parameters remained within normal limits, and there was no change in attitude, appetite, or manure production throughout the duration of the study.

Hematologic monitoring

CBC and selected biochemical parameters remained within normal limits throughout the study in all horses. Coagulation parameters are summarized (Table 1).
Discussion

The findings of this study failed to reject the null hypothesis that neither flunixin meglumine nor firocoxib would result in a significant alteration of viscoelastic coagulation profiles in healthy horses. While there was a statistically significant difference over time and between treatments for 2 parameters (A20 and MCF), A20 and MCF represented clot firmness (at 20 minutes and maximum firmness before clot lysis began, respectively), with higher values indicating better clot quality. Both parameters were higher in during treatment with flunixin meglumine than firocoxib, suggesting stronger clot formation. However, values for both parameters remained within reference intervals and the magnitude of difference was unlikely to be clinically significant.

Both PT and PTT were significantly increased in samples obtained pre- and post-treatment with flunixin meglumine. However, it is suspected that this was an artifact secondary to prolonged storage of citrated plasma from the flunixin meglumine treatment week, as no horses showed signs of coagulopathy during the study. Storage of citrated plasma at –20 °C for ≥6 months has been shown to artifactually increase both PT and PTT. Due to limitations in the design of this crossover study, there was prolonged storage of the plasma from the flunixin meglumine treatment period, likely resulting in increased PT and PTT results.

While there was a statistically significant increase in fibrinogen following treatment with flunixin meglumine, the magnitude of this change was not clinically significant. A single individual was above the upper end of the reference range (fibrinogen, 281 mg/dL; normal, 125 to 262 mg/dL); all other individuals were within normal limits.

Horses in this study were administered omeprazole prophylactically to mitigate the risk of gastric ulceration with NSAID administration. An association between omeprazole and drug-induced coagulopathy in human patients has recently been identified in postmarketing data. However, a causative relationship has not been established. To the authors’ knowledge, omeprazole-associated coagulopathy has not been reported in horses, and it is unlikely that the effect of flunixin meglumine and firocoxib on coagulation would have differed in the absence of omeprazole.

The findings reported here are limited to systemically healthy horses, as the relationship between COX inhibition and coagulation homeostasis may differ in horses with ongoing inflammation or predisposed to coagulopathy. NSAID administration was limited to short term (5 days), and it is possible that prolonged treatment would have further impact on coagulation homeostasis. Additional investigation in
a large population including clinically ill horses and horses on long-term firocoxib should be considered. Due to drug availability, flunixin meglumine was administered IV while firocoxib was administered PO, which may have confounded study outcomes.

In conclusion, short-term administration of flunixin meglumine and firocoxib to healthy adult horses did not result in significant alteration of viscoelastic coagulation profiles. However, clinicians should be aware of coagulopathy-associated adverse effects of COX-2–selective NSAIDs in other species, and further study is warranted.

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