A PLACEBO-CONTROLLED STUDY OF THE CLINICAL SAFETY OF AN ORAL FORMULATION OF DIPYRONE IN HORSES

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INTRODUCTION

Dipyrone

Dipyrone is a novel non-steroidal drug (NSAID) also known as metamizole in Europe.

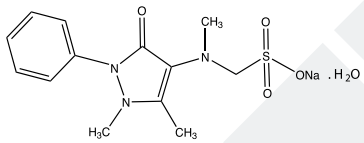
Dipyrone is a prodrug, which is converted to active metabolites with analgesic, antipyretic, and anti-spasmodic effects.

Compared to other drugs in the NSAID class, dipyrone is well tolerated with respect to gastrointestinal side effects.

Dipyrone is available as an injectable formulation in Europe; however, no oral formulation which is bioavailable has been developed for use in horses.

The commonly accepted dose is 30 mg/kg administered intravenously (IV) [1].

Figure 1. Chemical structure of dipyrone



Molecular Formula: $C_{13}H_{16}N_3NaSO_4.H_2O$

Molecular Weight: 351 g/mol

OBJECTIVE

This study evaluated the clinical safety of a high dose oral formulation of dipyrone in horses.

METHODS

This study was an unmasked, pilot study.

Seven horses were randomized in two treatment groups.

The dipyrone group was treated with a novel gel formulation containing 80 mg/kg dipyrone orally via a catheter tip syringe twice daily for 15 days.

Placebo-treated horses received saline on the same schedule.

Inclusion/Exclusion

- No evidence of gastrointestinal, renal or hepatic disease and no relevant clinical pathology abnormalities during acclimation
- No history of sensitivity to NSAIDs
- Gastric ulcer number and severity score < 1

METHODS (CONT'D)

Figure 2. Mechanism of fever in the horse

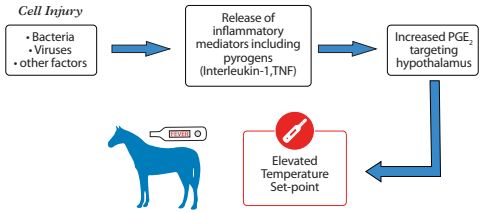


Table 1. Schedule of events

Study Day	Clinical Observations	Health Evaluation[1]	Oral Exam & Gastroscopy[2]	Treatment
-14 to -1	X			
-12		X		
-7			X	
-1		X[3]		
0 to 14	X, X			X, X
8		X	X	
15	X, X	X	X	

[1] Health evaluations included physical examination (PE), body weight (BW) measurements, collection of blood samples for hematology and serum chemistry

[2] Horses were fasted for a minimum of 12 hours prior to gastroscopy

[3] PE and BW only

RESULTS

Horses

Seven mature, intact female horses, 7 to 12 years of age, ranging from 439 to 544 kg body weight were enrolled.

Safety

Two dipyrone-treated horses and one placebo horse showed oral mucosal trauma that was related to syringe dosing.

One placebo horse had a mild episode of colic on study Day 9 that resolved uneventfully.

One dipyrone-treated horse had a clinically significant increase in creatine kinase (CK) and aspartate aminotransferase (AST) beginning on Day 8 and remained unchanged throughout the study.

One dipyrone-treated horse had a clinically significant increase in CK at study termination.

RESULTS (CONT'D)

Table 2. Gastroscopy observations

Horse	Treatment	Gastric Ulcer Number/Description		
		Baseline	Day 8	Day 15
458	Dipyrone	0	0	1-2 lesions/ mucosa only
577	Dipyrone	0	0	0
802	Dipyrone	0	0	0
818	Dipyrone	0	0	0
821	Dipyrone	1-2 lesions/ mucosa only	0	1-2 lesions/ mucosa only
634	Placebo	0	0	0
814	Placebo	0	0	0

Figure 3. Normal stomach

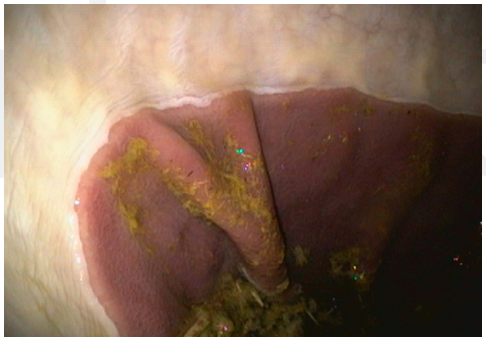
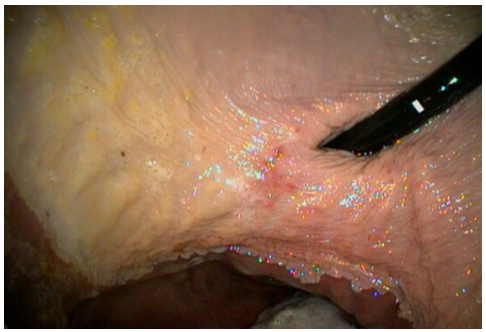


Figure 4. 1-2 lesions/mucosa only



DISCUSSION

No serious adverse events were recorded and none of the reported adverse events were considered related to dipyrone.

The clinical pathology abnormalities in two horses were mild and attributed to possible muscle damage and not considered related to dipyrone.

The two treated horses that had gastric ulcer scores of 1 on Day 15 were considered to be consistent with environmental stress or anorexia related to the procedure and not related to dipyrone. A score of 1 is not considered clinically relevant and not expected to cause clinical symptoms.

CONCLUSIONS

High dose dipyrone was well tolerated in horses when administered twice daily for 15 days.

Clinical pathology parameters did not reveal any toxicologic changes due to dipyrone administration.

Gastroscopy findings supported that high dose oral dipyrone in this novel formulation does not induce gastric ulcers in healthy horses.

DISCLOSURES

Emily Sundman and Melinda Poole are employees of Kindred Biosciences, Inc.

Craig Reinemeyer is a contractor for Kindred Biosciences, Inc.

REFERENCES

1. Sundman E, Ming Y, Hu T et al. Double-blind, placebo-controlled, randomized study of dipyrone as a treatment for pyrexia in horses. 2016. AAEP Proc Vol 62: p 228-29.

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