A RANDOMIZED, BLINDED, PLACEBO-CONTROLLED CROSSOVER STUDY OF DIPYRONE TO CONTROL FEVER IN HORSES

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INTRODUCTION

Dipyrone

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

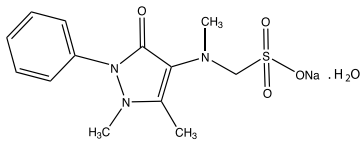
Dipyrone is a prodrug, which is converted to active metabolites with analgesic, antipyretic, and anti-spasmodic effects.

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

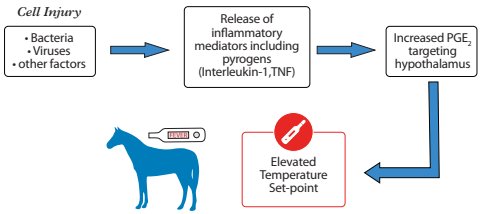
This study evaluated the efficacy of dipyrone administered intravenously to control fever in horses compared to placebo.

METHODS

This was a blinded, randomized, placebo-controlled pilot study with two treatment groups conducted at a single site.

Thirty-one horses with fever (rectal temperature ≥ 102.0°F) from naturally occurring disease were randomized in two treatment groups.

Figure 2. Mechanism of fever in the horse



METHODS (CONT'D)

PHASE I

The dipyrone group was treated with a single dose of 30 mg/kg dipyrone IV.

The placebo group was treated with a single matched volume dose of 0.9% sodium chloride IV.

PHASE II

Horses were crossed over to the other treatment group if they had a rectal temperature of ≥102°F 24 to 30 hours following treatment in Phase I.

	Phase I	Phase II
Dipyrone	Group 1	Group 2
Placebo	Group 2	Group 1

Rescue Medication

- Eligible if fever ≥ 105.0°F for 8 consecutive hours after dose 1
- Antibiotics allowed immediately and a NSAID administered 8 hours after last dose of study drug

Assessments

- Rectal temperature at 0, 4, 6 and 24 hours after treatment administration

Response Definition

- Decrease in rectal temperature of either ≥ 2.0°F from baseline or a return to normothermia (≤ 101.0°F) 6 hours after treatment

Statistical Comparison

- Between groups using a two-sided Fisher's Exact Test

RESULTS

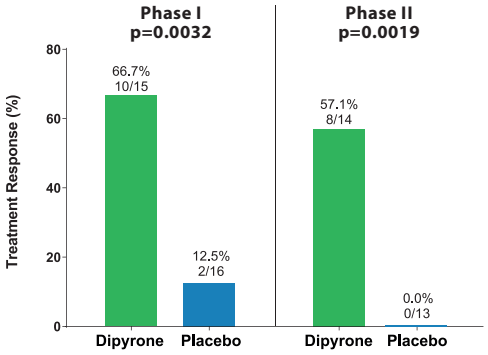
Phase I: 15 horses treated with dipyrone and 16 horses treated with placebo

Phase II: 14 horses treated with dipyrone and 13 horses treated with placebo

Sex	Appoximate Mean age	Breed
Male Castrated: 10 Female intact: 21	8 years (range 3-20)	13 Tennessee Walking Horses (TWH) 13 Quarter Horses 4 Paint Horses 1 Mixed TWH/Paint

RESULTS (CONT'D)

Figure 3. Treatment response rate



Response: decrease in rectal temperature of either ≥ 2.0°F from baseline or a return to normothermia (≤ 101.0°F) 6 hours after treatment

Figure 4. Mean temperature over time

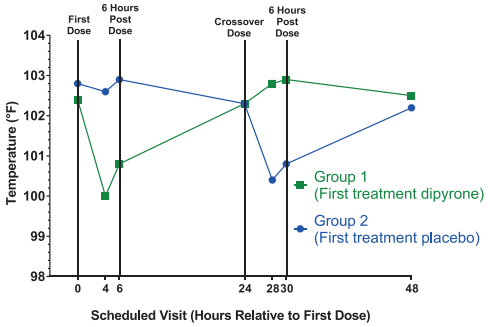


Table 1. Response at 6 hours following the first dose and crossover dose

Response Criteria	Horses n (%)
Response with dipyrone and placebo (+,+)	0 (0)
Non-response with dipyrone and placebo (-,-)	10 (37)
Response with dipyrone; non-response with placebo (+,-)	17 (63)
Non-response with dipyrone; response with placebo (-,+)	0 (0)
Total*	**27 (100)**

*Includes horses which had both the first and crossover treatment

DISCUSSION

Dipyrone administered IV at 30 mg/kg effectively reduced pyrexia in 10 of 15 horses in Phase I and 8 of 14 horses in Phase II. The findings of the combined Phase I and Phase II results show that dipyrone was effective in controlling fever in 18/29 horses.

The placebo response rate in Phase 1 (2/16 horses) is consistent with the placebo response rate found in evaluating fever in horses [1]. Additionally, horses in Phase II had additional time for the underlying disease to progress, which is indicated by the lack of response in placebo treated horses in Phase 2.

Treated horses did not exhibit adverse events related to dipyrone administered IV at 30 mg/kg and all reported adverse events were expected and considered related to the underlying disease process.

CONCLUSIONS

A single dose of dipyrone IV effectively controlled fever for 6 hours post administration and was superior to placebo.

The measured anti-pyretic effect was maximized at approximately 4 hours post administration.

Dipyrone was well tolerated in horses with naturally occurring respiratory disease.

DISCLOSURES

Ryan Avenatti, Ming Yin, Tianhua Hu, Melinda Poole, and Emily Sundman are/were 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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