Double-Blind, Placebo-Controlled, Randomized Study of Dipyrone as a Treatment for Pyrexia in Horses

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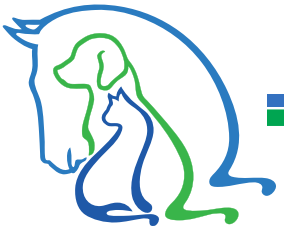
Disclosures

- Sundman, Yin, Hu, and Poole are employees of KindredBio
- KindredBio sponsored the study as part of a new animal drug approval (NADA) application to FDA-CVM
- Clinical Investigators received standard compensation for study-related procedures and activities. Owners were not compensated directly; however, the costs of study-related diagnostics were covered by KindredBio in an effort to support Clinical Investigators in decisions regarding enrollment and treatment

Ethical Considerations – The Speaker has adhered to AVMA's Principle of Veterinary Medical Ethics



Dipyrone History

- Dipyrone is an atypical NSAID used in veterinary animals and humans (Europe, South America) for the control of pyrexia
- Dipyrone has not previously been approved by FDA-CVM for use in horses
- Dipyrone was removed from the US market in 1995 following reports of extra-label use in food animals

Currently, there are no FDA approved medications labelled to control pyrexia in horses

Study Design

The Study was divided into two phases:

1) Randomized, placebo controlled, blinded study to evaluate effectiveness of dipyrone in febrile horses (Hour 0-Hour 6)
2) Open-label, unblinded study to evaluate safety of dipyrone in horses (Hour 6-Day 3/5)

Enrollment Criteria:

- Fever (≥102.0°F)
- Aged >12 months
- Met medication washout requirements
- Not pregnant or lactating
- Received Owner Consent
- Free of severe systemic disease that would interfere with study
- Reasonably expected to complete first 6 hrs of study
- Be manageable and cooperative with study procedures

Study Activities

Effectiveness Phase Activities

Met Enrollment Criteria, complete Physical Exam, collect blood

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Randomized 3:1 (dipyrone:placebo)

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Rectal temp recorded within 1 hr before treatment

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Treated with 30 mg/kg dipyrone IV or matched placebo

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Rectal temp recorded 6 hrs following treatment

Safety Phase Activities

Demonstrated Effectiveness at Hour 6

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Treat with concomitant medications and complete diagnostic testing

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Treat with 30 mg/kg dipyrone IV, as needed, up to three times daily

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Complete Physical Exam and collect blood at Day 3/5

Primary Endpoint

- The primary endpoint was control of pyrexia as defined by a rectal temperature change from Hour 0 to Hour 6 of either:

    1) decrease of 2°F or greater

    2) decrease to normothermia (≤ 101.0°F)

Results - Population

- 14 clinical sites enrolled cases in 12 states
- 138 horses were enrolled
  - Median Age 3 years
  - 13.8% Stallions, 32.6% Geldings, 53.6% Mares
  - 59.4% Quarter Horse, 10.1% Paints, 5.1% Arabian, and 5.1% Thoroughbred
  - Median Body Weight 364 kg

Results - Diagnoses

Diagnosis Category	Dipyrone (n=104)	Placebo (n=34)
Bacterial Respiratory Infection	43	16
Bacterial & Viral Respiratory Infection	25	9
Viral Respiratory Infection	9	2
Immune Mediated Cause	8	2
Musculoskeletal Infection	5	1
Tick-borne Infection	5	1
Fever of unknown origin	3	0
Viral Gastrointestinal Infection	0	1
Localized Bacterial Infection	1	0
Localized Infection	1	0
Colic	1	0
Bacterial Respiratory & Generalized Infection	0	1
Bacterial Respiratory Infection & Tick-borne Infection	1	0
Immune Mediated Cause & Generalized Bacterial Infection	1	0
Viral Respiratory Infection & Other Undefined Diagnosis	1	0
Bacterial & Viral Respiratory Infection with Local Infection	0	1

Results – Effectiveness Phase

	Dipyrone n (%)	**Placebo n (%)**	**P-value**
Population			
Treated Population	104 (75.4%)	34 (24.6%)	
Evaluable Population	99 (76.2%)	31 (23.8%)	
Statistical Evaluation			
Demonstrated Effectiveness	76 (76.8%)	6 (19.4%)	<0.0001

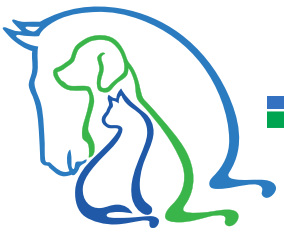
Results - Dose

	Horses
Completed Effectiveness Phase	138
Demonstrated Effectiveness in Effectiveness Phase	85
Continued to Safety Phase	87
Received dipyrone in Safety Phase	59

	Number of Dipyrone Doses
Total Safety Phase Doses	154
Total Safety Phase Doses Day 2	55
Total Safety Phase Doses Day 3	49
Mean Safety Phase Dose/Horse	1.8
Range Dose/Horse	0-8

Results - Safety, Observations

Adverse Event (Observations)	Dipyrone (n=107)	Placebo (n=34)
Any adverse event	32 (29.9%)	9 (26.5%)
Loose stool	3 (2.8%)	1 (2.9%)
Nasal discharge	2 (1.9%)	1 (2.9%)
Injection site reaction	2 (1.9%)	0 (0.0%)
Local swelling	1 (0.9%)	3 (8.8%)
Anorexia	1 (0.9%)	1 (2.9%)
Diarrhea	1 (0.9%)	1 (2.9%)



Results - Safety, Clinical Pathology

Adverse Event (Clinical Pathology)	Dipyrone (n=107)	Placebo (n=34)
Monocytosis	5 (4.7%)	1 (2.9%)
Increased sorbitol dehydrogenase	3 (2.8%)	1 (2.9%)
Leukocytosis	3 (2.8%)	1 (2.9%)
Lymphopenia	3 (2.8%)	1 (2.9%)
Elevated fibrinogen	2 (1.9%)	1 (2.9%)
Anemia	2 (1.9%)	0 (0.0%)
Elevated total bilirubin	2 (1.9%)	0 (0.0%)
Hyperglycemia	2 (1.9%)	0 (0.0%)
Hyperphosphatemia	2 (1.9%)	0 (0.0%)
Lymphocytosis	2 (1.9%)	0 (0.0%)
Coagulation abnormality	2 (1.9%)	0 (0.0%)
Neutrophilia	1 (0.9%)	1 (2.9%)

Results - Safety

Two horses were euthanized during the study, due to underlying diseases that were unrelated to dipyrone treatment

- Colic, confirmed strangulating lipoma at necropsy
- Septic arthritis

Results – Clinical Pathology Statistics

Clinical Pathology Parameter	LS Means (SEM) Dipyrone (n=106)	Placebo (n=31)	Reference Range
Neutrophil count (cells/µL)	6670 (297)*	7780 (550)†	2460-7230
Platelet count (k/µL)	215 (6.9)*	240 (13)	100-350
Prothrombin time (sec)	9.6 (0.06)*	9.9 (0.11)	8.9-11.9
Aspartate aminotransferase (U/L)	247 (4.0)*	261 (7.6)	194-431
Creatine kinase (U/L)	232 (22)*	336 (40)	130-497

*Statistically significant differences at level $p \leq 0.1$ between dipyrone and placebo

†LS mean value outside of reference range

Results – Clinical Pathology

Clinical Pathology Parameter	Mean (SD) Dipyrone (n=106)	Placebo (n=31)	Reference Range
Hematocrit (%)	31.8 (5.4)*	31.9 (5.4)*	32.5 - 46.5
Monocyte count (cells/µL)	741 (330)*	779 (421)*	0 - 600
Neutrophil count (cells/µL)	6644 (3655)	7871 (4384)*	2460 - 7230
Partial thromboplastin time (sec)	47.6 (9.5)*	49.4 (8.4)	48.0 - 77.0
Albumin (g/dL)†	2.8 (0.5)*	2.8 (0.4)*	3.0 - 3.9
Globulin (g/dL)	4.3 (1.0)*	4.2 (0.9)*	2.3 - 4.1

*Clinical pathology parameters outside of reference range at study termination in horses treated with one to nine doses of dipyrone or one dose of placebo

Conclusions

- Dipyrone effectively controls fever in horses given a single dose of 30 mg/kg IV
- There were few adverse events in horses treated with dipyrone in the effectiveness or safety phase of the study
- The majority of adverse events were mild and primarily related to the underlying disease
- The number of doses administered in the safety phase was unexpectedly low, and likely due to the use of concomitant medications in the safety phase, including antibiotics
- The majority of horses enrolled in the study were febrile due to a viral or bacterial respiratory disease common within the adult horse population