

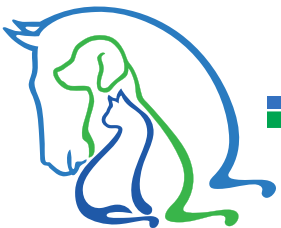
Double-Blind, Placebo-Controlled, Randomized Study of Dipyrone as a Treatment for Pyrexia in Horses

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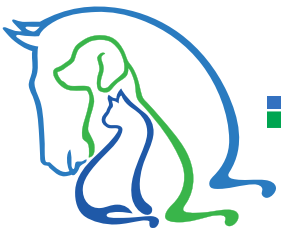
Melinda Poole, DVM



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

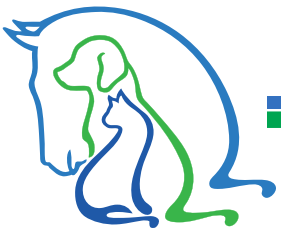
Ethical Considerations – The Speaker has adhered to AVMA's Principle of Veterinary Medical Ethics



Dipyron History

- Dipyron is an atypical NSAID used in veterinary animals and humans (Europe, South America) for the control of pyrexia
- Dipyron has not previously been approved by FDA-CVM for use in horses
- Dipyron 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



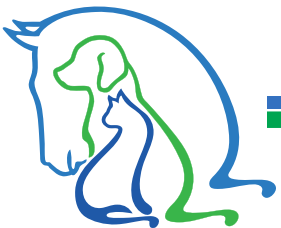
Study Design

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 ($\geq 102.0^{\circ}\text{F}$)
- 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



Randomized 3:1 (dipyron:placebo)



Rectal temp recorded within 1 hr before treatment



Treated with 30 mg/kg dipyron IV or matched placebo



Rectal temp recorded 6 hrs following treatment

Safety Phase Activities

Demonstrated Effectiveness at Hour 6



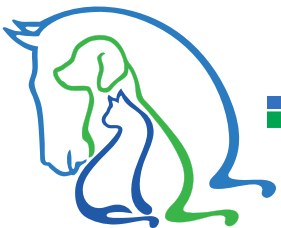
Treat with concomitant medications and complete diagnostic testing



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

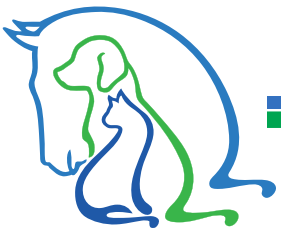


Complete Physical Exam and collect blood at Day 3/5



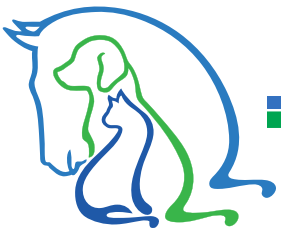
Primary Endpoint

- 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 ($\leq 101.0^{\circ}\text{F}$)



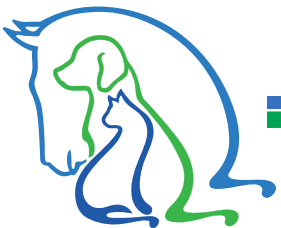
Results - Population

- 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



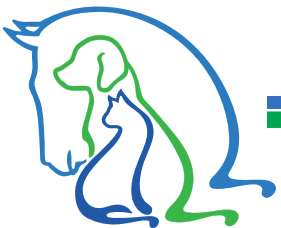
Results - Diagnoses

Diagnosis Category	Dipyron (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



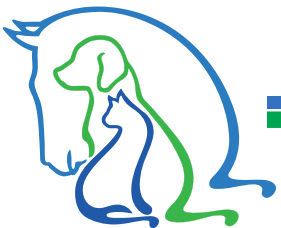
Results – Effectiveness Phase

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



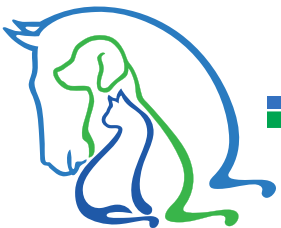
Results - Dose

	<u>Horses</u>	
Completed Effectiveness Phase	138	
Demonstrated Effectiveness in Effectiveness Phase	85	
Continued to Safety Phase	87	
Received dipyron in Safety Phase	59	
		<u>Number of Dipyron Doses</u>
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



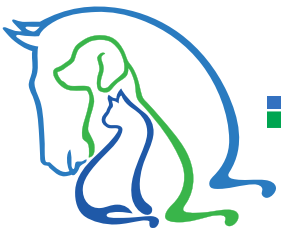
Results - Safety, Observations

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

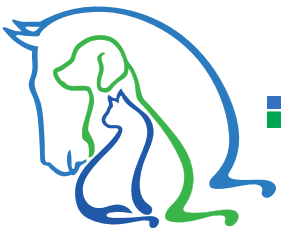
Adverse Event (Clinical Pathology)	Dipyrrone (n=107)	Placebo (n=34)
Monocytosis	5 (4.7%)	1 (2.9%)
Increased sorbitol dehydrogenase	3 (2.8%)	1 (2.9%)
Leukocytosis	3 (2.8%)	1 (2.9%)
Lymphopenia	3 (2.8%)	1 (2.9%)
Elevated fibrinogen	2 (1.9%)	1 (2.9%)
Anemia	2 (1.9%)	0 (0.0%)
Elevated total bilirubin	2 (1.9%)	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 dipyron treatment

- Colic, confirmed strangulating lipoma at necropsy
- Septic arthritis

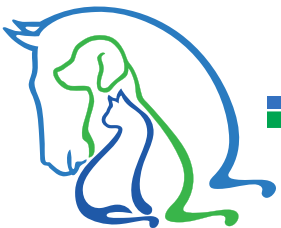


Results – Clinical Pathology Statistics

Clinical Pathology Parameter	LS Means (SEM)		Reference Range
	Dipyrrone (n=106)	Placebo (n=31)	
Neutrophil count (cells/ μ L)	6670 (297)*	7780 (550) [†]	2460-7230
Platelet count (k/ μ L)	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 dipyrrone and placebo

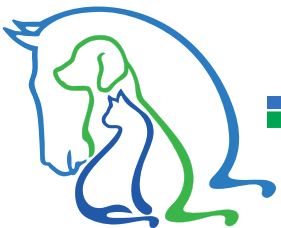
[†]LS mean value outside of reference range



Results – Clinical Pathology

Clinical Pathology Parameter	Mean (SD)		Reference Range
	Dipyron (n=106)	Placebo (n=31)	
Hematocrit (%)	31.8 (5.4)*	31.9 (5.4)*	32.5 - 46.5
Monocyte count (cells/ μ L)	741 (330)*	779 (421)*	0 - 600
Neutrophil count (cells/ μ L)	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 dipyron 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

