Review: The use of phenylbutazone in the horse

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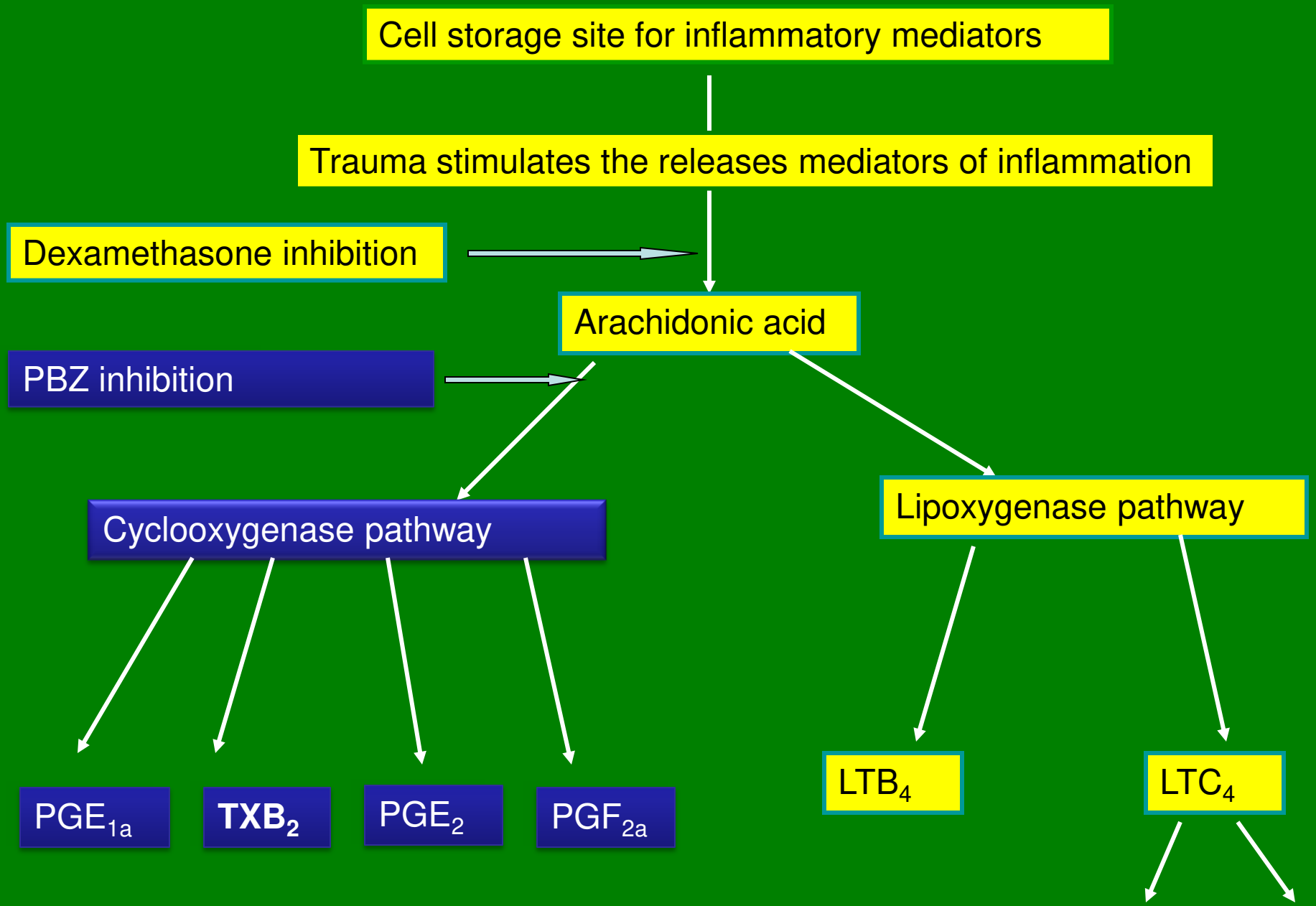
Cell storage site for inflammatory mediators
Trauma stimulates the releases mediators of inflammation
Dexamethasone inhibition
Arachidonic acid
PBZ inhibition
Cyclooxygenase pathway
Lipoxygenase pathway
PGE1a
TXB2
PGE2
PGF2a
LTB4
LTC4

PBZ historical background

- Phenylbutazone was introduced into veterinary medicine in the 1950's (Tobin et al., 1986) and still remains one of the more commonly used NSAID in horse racing.
- Controversy in late 70's "Baker yellow book"
- In 1977 the National Association of State Racing Commissioners Veterinary-Chemist Advisory board concluded that "phenylbutazone is a safe effective nonsteroidal anti-inflammatory drug (NSAID) with antipyretic and analgesic activity. In recommended doses, there is no evidence that it changes a horse's innate ability to race, except to make him perform more nearly normal if he has pain due to inflammation of part of his musculoskeletal system" (Gabel et al., 1977).
- PBZ has no clear effect on the performance of the normal horse, as their actions depend on anti-inflammatory effects (Sanford, 1974; Bogan, 1983; Hinchcliff et al., 1994)

- Conclusion of many veterinarians was that it would allow a horse to compete with mild chronic arthritic changes.
- Not sufficient analgesia to allow a horse with a serious injury to compete.
- Number of studies were completed to determine the concentrations at 24 hours following various dose schedules (Soma et al 83, 85 Chay, et al 84; Houston et al.,1985;).
- Recommended dosing schedule: oral for at least 3 days followed by the IV dose of 2 grams 24 h prior to the race.
- Concentration on race day should not exceed 5 µg/ml
- The American Association of Equine Practitioners recommends a dose of 2.2mg/kg daily with the last dose not more than 24 hours prior to post time (Harvey 1983)

Questions

- Does that administration schedule used have and effect on race day?
- Is there information available that can help answer that question?
- What are the long term consequences of the continuous administration of PBZ?
- Are we boxed in the treatment of a horse based on our rules of racing?

Effects of Phenylbutazone on Naturally Occurring Osteoarthritic Disorders

- Chronic forelimb lameness - force plate & AAEP lameness Score (Hu et al., 2005)
  - PBZ **4.4 or 8.8 mg/kg** IV daily for 4 days.
  - Force plate 6 ,12, 24 h for both doses
  - Higher dose did not effect scoring, just duration.

- Navicular syndrome - force plate analysis and AAEP lameness scoring (Erkert et al., 2005)
  - Flunixin (**1.1 mg/kg**), PBZ (**4.4 mg/kg**), or saline IV (6 ,12, 24, 30 h evaluation)
  - Effect of flunixin and PBZ was maintained for 24 hours not to 30
  - Flunixin & PBZ equally effective.

- Chronic laminitis - bilateral forelimb. Electric hoof tester and subjective scoring.
  - Phenylbutazone (**4.4 mg/kg**) and ketoprofen (**3.63 mg/kg**) were still effective at 24 h lower dose of ketoprofen (**2.2 mg/kg**) no effect at 24 hours (Owens, Kamerling et al. 1995).

- Navicular disease - force plate evaluation. Treatment was heal elevation and PBZ
  - Improvement with heal elevation.
  - Further improvement 24 h following PBZ (**4.4 mg/kg, IVq 12 h**) for 5 days (Schoonover, Jann et al. 2005).

Effects of phenylbutazone on an induced lameness models (reversible).

- Adjustable bar shoe model of equine foot pain - PBZ IV dose (**4.4 mg/kg**) (Foreman et al., 2008).
  - At maximum effect, the lameness score was reduced from 4 to 1.5 score at 4 to 5 h.
  - Plasma concentrations were15 and 7 µg/ml at 4 and 8 h.
  - Lameness score had not returned to baseline response at 9 h.
- Lipopolysaccharide-induced synovitis.
  - PBZ (**4.4 mg/kg**) and flunixin (**1.1mg/kg**) peak effect occurred between 8-12 h.
  - Flunixin analgesic activity persisted for 30 hours and PBZ for 24 hours

Indirect assessment - plasma

- Inhibitory actions of NSAIDs on inflammatory mediators following a single dose of flunixin (**1.1 mg/kg**) or PBZ (**4.4 mg/kg)** (Lees et al., 1987).
  - At 24 h 63 & 50 % reduction of TBX_2 for flunixin and PBZ.
  - At 48 hours inhibition was no longer apparent.

- Inhibitory actions of NSAIDs on inflammatory mediators following Flunixin (**1.1 mg/kg)** & PBZ (**2.2 mg/kg**) in combination & single administration (Semrad et al., 1993).
  - Inflammatory mediators suppressed for 12, 8, and 24 hours after combination
  - PBZ (**2.2 mg/kg**) administered alone the inflammatory mediators were not significantly different from control at 24 h.

Indirect assessment - exudates

- Studies of inflammatory mediators at the site of inflammation (Higgins 1984).
  - Significant reduction of products of metabolism at 6, 12, & 24 hours
  - PBZ plasma concentration lower than PBZ concentrations at site of inflammation.
- Similar conditions occurring in an inflamed joint.
  - Amount of drug in joint vs. plasma related to the degree of inflammation.

Long term effects

- Potential negative consequences on long-term use and the healing process are slowly growing (Fournier, Leal et al. 2008).
- Dependent on injury – stress fracture vs. tendonitis.
- Short-term use for analgesic purposes
- There is limited information on synovial membrane health in the horse and many of the studies were conducted in-vitro.
- Chronic administration may potentiate cartilage damage (Beluche, Bertone et al. 2001).
- COX-2 inhibitor diclofenac induced significantly *less cartilage erosion*, compared with PBZ.
- We are boxed in to 2 drugs .

Conclusion

- Studies indicate an effect of PBZ at 24 hours at 2 grams
- Lower concentrations of 2 drugs - additive effect
- Studies confirm the opinion of many veterinarians not to examine a horse for lameness if administered NSAID or glucocotricoid.
- Little information on long term effects of continuous administration of NSAIDs
- Should allow more diverse medication policies.
- Effect on catastrophic injuries problematic.
- Fewer starts per horse?

Thank you

- Remember the message does not change if you kill the messenger.

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  - Pennsylvania Horse and Harness Racing Commissions and in part by
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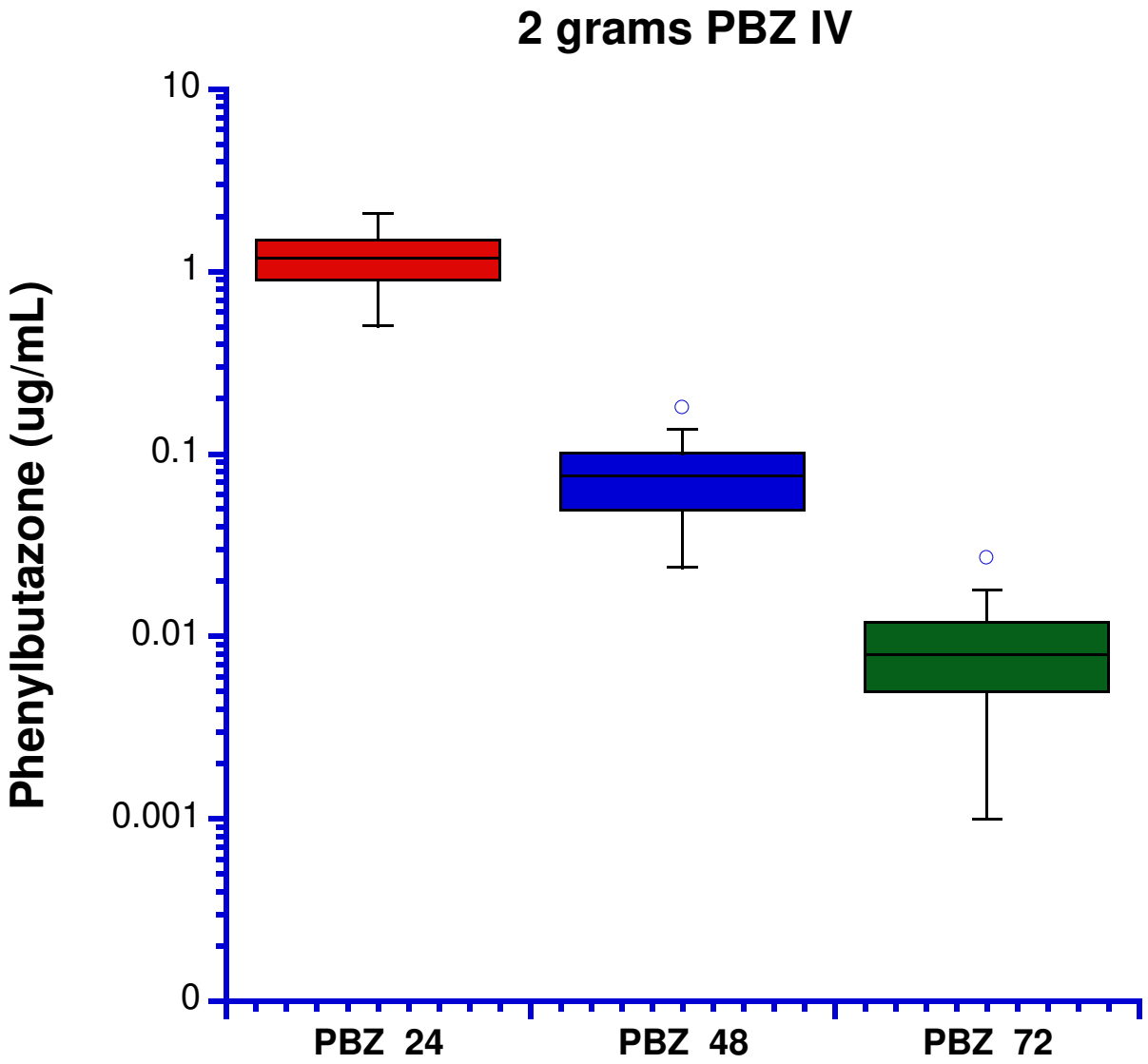
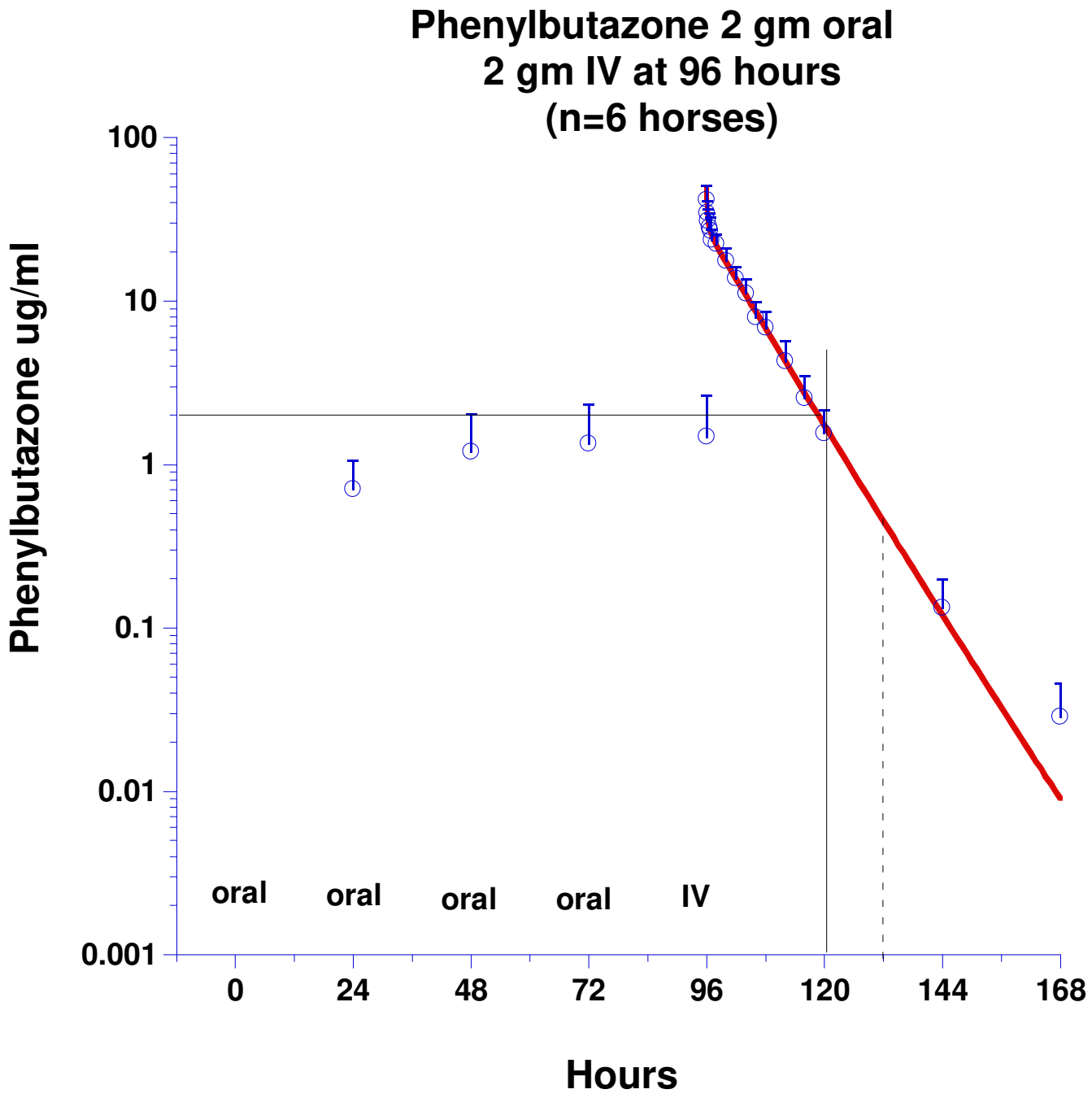
  - Pennsylvania Harness Horsemen Association
  - Meadows Standardbred Owners Association.


2 grams PBZ IV
Phenylbutazone (ug/mL)
10
1
0.1
0.01
0.001
0
PBZ 24
PBZ 48
PBZ 72


Phenylbutazone 2 gm oral
2 gm IV at 96 hours
(n=6 horses)
Phenylbutazone ug/ml
100
10
1
0.1
0.01
0.001
oral
oral
oral
oral
IV
0
24
48
72
96
120
144
168
Hours

Indirect assessment of duration of action

- Vane in 1971 suggested the mechanism of the action of aspirin like compounds was a direct inhibition of prostaglandin synthetase and preventing prostaglandin biosynthesis (Vane, 1971; Moncada et al., 1974; Moncada et al., 1975; Vane and Botting, 1987)
- Many studies have been published using reduction in the metabolic products of inflammation in plasma as an indication of the duration of action of PBZ and other NSAID'S (Lees et al., 1987a; Soma et al., 1992; Lees et al., 2004a; Lees et al., 2004b)
- Others have used tissue cage and sponge models (Higgins and Lees, 1984; Lees and Higgins, 1984; Higgins et al., 1987; Lees et al., 1987b).
- Recently models in humans have used flow through methods to harvest inflammatory exudate from non-inflamed and experimentally inflamed skin (Angst et al., 2008a; Angst et al., 2008b)

Continued

- 12-day treatment schedule ponies were given PBZ orally paste or placebo paste (Lees and Higgins, 1986).
  - On day 12, a mild, non-immune inflammatory reaction was induced subcutaneously.
  - Exudate was collected at 4, 8, 12, and 24 hours.
  - There were no significant differences in exudate protein concentration and leukocyte numbers
  - PBZ had significantly reduced exudate concentrations of 6-ketoF1α at 4, 8, and 12 hours;
  - TBX_2 at 8, 12, and 24 h.
  - Increases in surface skin temperature were significantly less in PBZ treated between 4 and 24 hours