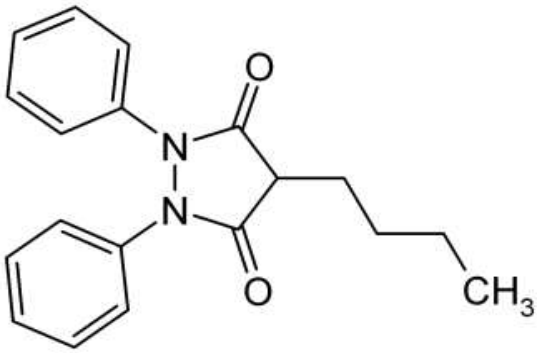
CONTROLLED THERAPEUTIC MEDICATIONS
MONOGRAPH SERIES

Phenylbutazone

Background



https://commons.wikimedia.org/wiki/File:Phenylbutazone.png

Phenylbutazone is among the oldest and most commonly used non-steroidal anti-inflammatory (NSAID) in veterinary medicine.[i] It is assigned 4/C in the ARCI's Uniform Classification of Foreign Substances. Phenylbutazone is administered orally or intravenously for its anti-inflammatory, analgesic, and antipyretic effects.[ii] It is frequently used to control inflammation and pain resulting from osteoarthritis, navicular disease, and synovitis.[iii]

Phenylbutazone is a prescription medication and can only be dispensed by, or upon, the request of a veterinarian. It is commercially available as both a brand name and generic drug in a variety of formulations (injectable; and oral pastes, tablets, granules, and powders).[iv] Phenylbutazone can be administered intravenously and orally.[v] Doses range from 2.2 to 4.4 mg/kg every 12-24 hours for both the oral and parenteral routes.[vi]

Phenylbutazone is a non-selective cyclooxygenase (COX) inhibitor.[vii] It acts by inhibiting the portion of the arachidonic acid pathway responsible for production of thromboxanes, prostacyclins, and prostaglandins. The anti-inflammatory, anti-pyretic, and analgesic effects of phenylbutazone are believed to be associated with a reduction in prostaglandin synthesis.[viii] Additionally, researchers in one study concluded that phenylbutazone interferes with the expression of pleiotrophin that regulates migration of certain gastrointestinal cells – which may, in part, be responsible for an increase in gastric ulceration associated with use of phenylbutazone.[ix] In addition to the indirect cellular effects that phenylbutazone has on gastrointestinal mucosa, one group of researchers observed direct effects of oral phenylbutazone in altering the anti-oxidant/oxidant balance that may lead to additional ulceration in the stomach.[x]

When used judiciously, phenylbutazone can be beneficial in the treatment of, and recovery from, illness or injury. However, chronic administration or excessive doses of phenylbutazone are associated with significant side effects such as negative changes in blood and plasma

parameters[xi], gastrointestinal ulceration[xii], transient suppression of Type II cartilage[xiii], and nephrotoxicity[xiv]. One study recommended limiting use of phenylbutazone to a seven-day period to avoid gastrointestinal side-effects in horses.[xv]

Phenylbutazone Regulation

Phenylbutazone was historically regulated with a 5.0 micrograms(mcg)/mL in serum or plasma threshold that pre-dated the RMTC. In 2010 a revised threshold of 2.0 mcg/mL was adopted; it was intended to minimize the impact of phenylbutazone's anti-inflammatory effects on the pre-race exam. This revised threshold was not developed using a 95/95 tolerance interval but rather was founded on concerns that 5 mcg/mL of plasma or serum in a post-race sample allowed for a therapeutic effect at the time of the pre-race examination with the potential for unsoundness to be masked or obscured. The RMTC Scientific Advisory Committee (SAC) requested that Dr. Larry Soma prepare a summary of the research on phenylbutazone for review.[xvi] Based upon that review, the RMTC SAC determined that 2 mcg/mLof plasma or serum threshold was more appropriate to protect the horse.[xvii] In December 2019, the ARCI adopted a Model Rule that established a 48-hour restricted administration time (RAT) and a prohibition on stacking of NSAIDs (i.e. the detection of more than one NSAID in a blood and/or urine sample).

Administration Study

Twenty exercise-conditioned thoroughbred mares and geldings were administered a single 4.4 mg/kg IV dose of phenylbutazone. This administration study was performed at the University of Florida by personnel in the Equine Pharmacokinetics Laboratory under the direction of Dr. Patrick Colahan.

Blood samples were obtained immediately before dose administration and at the following times after dosing: 0.25, 0.5, 1, 2, 3, 4, 6, 8, 20, 24, 48, and 72 hours.

Extraction and Analysis Procedures

Quantification of phenylbutazone in plasma was performed at the University of Florida Racing Laboratory (Gainesville, FL) and the Maddy Equine Analytical Pharmacology Laboratory (Davis, CA) using validated methods similar to those previously described.[xviii] Phenylbutazone was determined in plasma by liquid chromatography-mass spectrometry (LC-MS/MS) using an internal standard to improve quantitative accuracy and precision. The Limit of Quantification (LOQ) for determination of phenylbutazone in plasma was 0.01 mcg/mL and the Limit of Detection (LOD) was 0.01 mcg/mL.

Pharmacokinetic Modelling

Pharmacokinetic analysis was performed on individual plasma concentrations using Phoenix® WinNonlin® pharmacokinetic analysis software (Pharsight Corporation, Cary, NC).

Results and Discussion

Mean plus standard deviation and median of the plasma concentrations after intravenous administration in all twenty horses are shown in table 1.1.

Table 1.1 Plasma phenylbutazone mean (±SD) and median values at select times following intravenous administration of 4.4 mg/kg of phenylbutazone to 20 horses

Time (hours)	Mean (±SD) (mcg/mL)	Median (mcg/mL)
24	0.95(±0.36)	0.977
48	0.06(±0.03)	0.071
72	0.01(±0.006)	0.014

Scientific Advisory Committee Recommendation

The plasma data from all 20 horses at the 48-hour collection time point were subjected to the 95/95 Tolerance Interval calculation which yielded a value of 0.283. The SAC rounded up to a threshold recommendation of 0.3 mcg/ mL of phenylbutazone in plasma based on a single IV dose of 4.4 mg/kg at 48 or more hours prior to post time.

Practice Tips

Administration of higher doses, use of oral administration, combinations of phenylbutazone with other substances, or serial administrations represent unknown risk for a concentration in excess of the threshold and therefore an extended withdrawal time is recommended. Veterinarians are advised to use caution when deviating from doses and routes that have been studied and to use an extended withdrawal time and/or submit a sample for analysis prior to competition.

The half-life of phenylbutazone has been shown experimentally to increase in horses over 10 years of age.[xix]

In a 2014 study, researchers determined that the use of phenylbutazone with furosemide caused a decrease in the efficacy of furosemide (urine volume and urine flow rate were 88% of control).[xx]

Veterinarians are advised to assess the potential impact of these factors on the withdrawal time for each individual horse and to advise their clients accordingly.

The prohibition on stacking of NSAIDs adopted into the Model Rules in 2019 is enforced through analysis of both blood and urine. When one NSAID is administered at 48-hours, an extended withdrawal interval must be observed for others to avoid a stacking violation. Veterinarians are advised to refer to the RMTC's Advisory on Non-steroidal Anti-inflammatory Drugs (NSAIDs): 48-hour Restricted Administration Time and Prohibition on Stacking for guidance.

References

[i] Soma, L.R. *et al.*, *The use of Phenylbutazone in the Horse*, J. Vet. Pharmacol. Therap. (2011) 35:1-12.

[ii] Sanchez, L.C. and Robertson, S.A.*, Pain Control in Horses: What do we Really Know?,* EVJ (2014) 46:517-23.

[iii] Sanchez, L.C. and Robertson, S.A., EVJ, 2014.

[iv] FDA Green Book. Available online at: https://animaldrugsatfda.fda.gov/adafda/views/#/search (Enter phenylbutazone in search box.)

[v] FDA Green Book.

[vi] Sanchez, L.C. and Robertson, S.A., EVJ, 2014

[vii] Erkert, R.S., *et al.*, *Use of Force Plate Analysis to Compare the Analgesic Effects of Intravenous Administration of Phenylbutazone and Flunixin Meglumine in Horses with Navicular Syndrome*, AJVR 2005;, 66(2):284-88.

[viii] Plumb, Donald. "Phenylbutazone." Plumb's Veterinary Drug Handbook. 8th ed. Stockholm: PharmaVet, 2015. 1150-53.

[ix] Silver, K., *et al.*, *Expression of Pleiotrophin, an Important Regulator of Cell Migration, is Inhibited in Intestinal Epithelial Cells by Treatment with Non-Steroidal Anti-Inflammatory Drugs*, Growth Factors (2012) 30(4):258-66.

[x] Martinez Aranzales, J.R., *et al.*, *Orally Administered Phenylbutazone Causes Oxidative Stress in the Equine Gastric Mucosa*, J. Vet Pharacol. Therap. (2014) 38:257-64.

[xi] McConnico, R.S., *et al.*, *Pathophysiologic Effects of Phenylbutazone on the Right Dorsal Colon in Horses*, AJVR (2008) 69(11):1496-504. *See also*, Reed, S.K., *et al.*, *Effects of Phenylbutazone Alone or in Combination with Flunixin Meglumine on Blood Protein Concentrations in Horses*, AJVR (2006) 67(3):398-402.

[xii] McConnico, R.S., *et al.*, 2008; Silver, K., *et al.*, *Expression of Pleiotrophin, an Important Regulator of Cell Migration, is Inhibited in Intestinal Epithelial Cells by Treatment with Non-Steroidal Anti-Inflammatory Drugs*, Growth Factors (2012) 30(4):258-66.

[xiii] de Grauw, J.C., *et al.*, *In Vivo Effects of Phenylbutazone on Inflammation and Cartilage-Derived Biomarkers in Equine Joints with Acute Synovitis*, The Veterinary Journal (2014) 201:51-

56 (concluding that phenylbutazone transiently interfered with production of type II collagen synthesis while failing to suppress inflammation-induced changes).

[xiv] Kivett, L., *et al.*, *Evaluation of the Safety of a Combination of Oral Administration of Phenylbutazone and Firocoxib in Horses*, J. Vet. Pharmacol. Therap. (2013) 37:413-16.

[xv] Nieto, J.E., *et al.*, *Effects of Phenylbutazone on Gene Expression of Cyclooxygenase-1 and -2 in the Oral, Glandular Gastric, and Bladder Mucosae of Healthy Horses*, AJVR (2012) 73(1):98-104.

[xvi] *See*, Soma, L.R., *et al.*, *The Use of Phenylbutazone in the Horse*, J. Vet Pharmacol. Therap. (2011) 35:1-12.

[xvii] Based upon experimental data, a 4.4 mg/kg dose of phenylbutazone whas significant analgesic effect in excess of 24 hours. *See*, Erkert, R.S., *et al.*, *Use of Force Plate Analysis to Compare the Analgesic Effects of Intravenous Administration of Phenylbutazone and Flunixin Meglumine in Horses with Navicular Syndrome*, AJVR (2005) 66(2):284-88.

[xviii] You, Y. *et al.*, *Screening, Quantification, and Confirmation of Phenylbutazone and Oxyphenbutazone in Equine Plasma by Liquid Chromatography-Tandem Mass Spectrometry*, J. of Analytical Toxicology (2009) 33:41-50.

[xix] Goodrich, L.R. and Nixon, A.J., *Medical Treatment of Osteoarthritis in the Horse – A Review*, The Vet. Journal (2004) 171:51-69.

[xx] Raidal, S.L., *et al.*, *Effects of Meloxicam and Phenylbutazone on Renal Responses to Furosemide, Dobutamine, and Exercise in Horses*, AJVR (2014) 75(7):668-79.