



Guaifenesin

Background

Guaifenesin is a centrally acting skeletal muscle relaxant that selectively depresses nerve impulse transmissions in the internuncial neurons of the spinal cord, brain stem, and subcortical regions of the brain.ⁱ It is assigned 4/C in the ARCI's Uniform Classification of Foreign Substances. Guaifenesin is commonly used as an adjunct to equine general short-term anesthesia and in racehorses to aid the clearance of mucus from the airways.

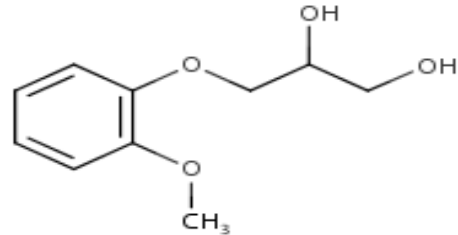


Figure 1: <https://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+3089>

Guaifenesin is available for human and equine use in over the counter oral powder or syrup formulations and by prescription as an injectable formulation. It is commercially available as Equi-Spectorant™ and Spec-Tuss™. Delivery method, dose, and frequency of administration are extremely variable and should be customized for each patient by the attending veterinarian.ⁱⁱ

Guaifenesin is often used in humans as an expectorant that exerts its effect by irritating the gastric mucosa which results in increased respiratory tract secretions and decreased mucus viscosity.^{iii,iv} Although the use of guaifenesin as an expectorant is not well studied in horses and claims of efficacy are anecdotal, it is still commonly used for that purpose in performance horses.^v

Perivascular injection can result in tissue necrosis. Hemolysis can occur following intravenous infusion, however the risk is minimal when the concentration of the solution is below 10%.^{vi} In concentrations at or above 10%, thrombophlebitis, venous thrombosis, and damage to vascular endothelium have also occurred. These adverse events may progress to periphlebitis, impaired venous drainage, embolism, or septicemia. Horses with abnormalities of hemostatic function are at increased risk for these effects.^{vii}

When used in anesthesia, guaifenesin induces the relaxation of skeletal muscles, facilitates a smooth transition to recumbency, and allows a reduction in the dose of other anesthetic drugs.^{viii} In concentrations below 10% the only clinical challenge is the large fluid volume required and thus an increased interval to onset of muscle relaxation and recumbency. The use of guaifenesin in combination with an ultra-short-acting barbiturate can provide a more rapid induction to

anesthesia and avoid the marked drop in arterial blood pressure, depressed respiration, or temporary apnea that occurs with the rapid injection of thiobarbiturates when used alone.^{ix}

Administration Study

A 2 g dose of guaifenesin powder (Spec-tuss, Neogen Corporation, Lexington, Kentucky) suspended in water was administered orally via dosing syringe BID for a total of five doses to nine healthy exercise-conditioned Thoroughbred horses (geldings and mares). This administration study was performed by personnel at Kentucky Equine Research (KER) in Versailles, Kentucky.^x

Blood samples were obtained immediately prior to administration and at 0.25, 0.5, 1, 2, 4, 6, and 12 hours following the first dose. Samples were also collected immediately prior to administration and at 0.25, 0.5, 1, 2, 4, 6, 12, 24, 36 and 48 hours after the final dose was administered. Additional samples were collected at 12-hour intervals, immediately before each administration, during the dosing period.

Extraction and Analysis Procedures

Quantification of guaifenesin in plasma was performed at the Maddy Equine Analytical Pharmacology Laboratory at the University of California, School of Veterinary Medicine, using validated methods. Guaifenesin plasma concentrations were determined in plasma samples using liquid chromatography-mass spectrometry (LC-MS/MS) using guaifenesin-d5 from Toronto Research Chemicals (Toronto, ON, Canada) as an internal standard in order to verify accuracy and precision. The Limit of Quantification (LOQ) for guaifenesin was 0.5 ng/mL and the Limit of Detection (LOD) was 0.3 ng/mL in plasma.

Pharmacokinetic Modeling

Plasma concentrations of guaifenesin are expressed as the mean, median, and range t 48 hours after the last administration (Table 1.1). Pharmacokinetic analysis was performed on all horses' individual plasma concentrations using Phoenix[®] WinNonlin[®] pharmacokinetic analysis software (Pharsight, Cary, NC).

Table 1.1 Mean ± SD, median and range of serum guaifenesin concentrations at 48 hours post-oral administration of 2 g BID for five doses to nine exercised Thoroughbred horses.

Time (h)	Mean ± SD (ng/mL)	Median (ng/mL)	Range (ng/mL)
48	0.3 ± 0.4	0.1	<LOD-0.9

Results and Discussion

Guaifenesin plasma concentrations were below the LOQ 36 hours after the final dose administration in six of the nine study horses. The guaifenesin concentrations in the three remaining horses were above the LOQ at 48 hours after the final dose. Overall, guaifenesin was rapidly absorbed following oral administration with peak plasma concentrations approximately 15 minutes after administration. Fluctuations in the plasma concentrations were large; very low concentrations were detected immediately prior to subsequent dosing, and bioaccumulation was not observed.

Scientific Advisory Committee (SAC) Recommendation

The 95/95 tolerance interval was calculated on the natural logarithmic (*i.e.*, ln) transformed plasma concentration data at 48 hours following the last 2 g oral dose of guaifenesin for all nine horses and resulted in a value of 10.3 ng/mL. The SAC recommended a threshold of 12 ng/mL of guaifenesin in plasma or serum. The corresponding withdrawal guideline is 48 hours based on a 2 g twice daily oral dose for five days. Administration of higher doses, alternative routes of administration, or combinations of guaifenesin with other substances may result in concentrations above the threshold unless an extended withdrawal time is observed.

Practice Tips

Guaifenesin is a metabolite of methocarbamol (MCBL) and therefore administration of methocarbamol may have a significant effect on the guaifenesin withdrawal time and plasma concentrations of a horse. Guaifenesin has been detected in plasma 8 hours following an oral dose of 5 g MCBL in one study and guaifenesin concentrations throughout said study mirrored the plasma concentrations of MCBL.^{xi} The co-administration of guaifenesin and methocarbamol warrants an extended withdrawal interval that considers the health of the individual horse, doses, routes of administration and treatment schedules for guaifenesin and methocarbamol.

Because bioaccumulation was not observed, it is not necessary to increase withdrawal intervals for administrations of 2 g guaifenesin PO BID for more than 5 doses.

References

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