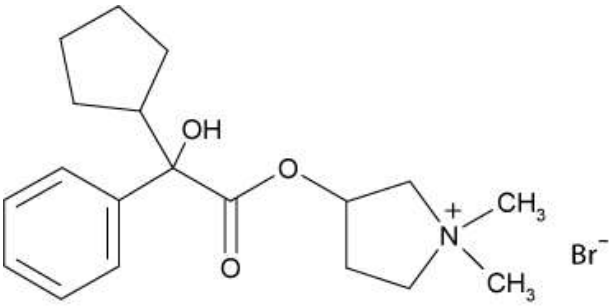
Glycopyrrolate

Background

Glycopyrrolate is a quaternary ammonium salt.[i] It is a synthetic anti-muscarinic substance with effects that are similar to atropine. Glycopyrrolate is assigned 4/C in the ARCI's Uniform Classification of Foreign Substances. Unlike atropine and some other anti-muscarinic compounds glycopyrrolate does not have significant effects on the central nervous system.[ii] It is often administered intravenously for decreasing secretions prior to anesthesia, treatment of equine asthma, for treatment of bradyarrhythmias, and may be used as an adjunct to imidocarb therapy.[iii] Anecdotally, glycopyrrolate has been used pre-work to reduce EIPH, but there is no empirical evidence of its efficacy for that purpose.



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Glycopyrrolate is a prescription medication and can only be dispensed by or used at the direction of a veterinarian.[iv] It is commercially available in a variety of formulations including Robinul™.[v] It is FDA approved for use in cats and dogs in intramuscular, subcutaneous, and intravenous formulations.[vi] Additionally, there are injectable and oral preparations that are FDA approved for use in humans.[vii] There is no FDA approved glycopyrrolate product available for use in the horse.

Glycopyrrolate is an anti-muscarinic. As such, it prevents acetylcholine from acting on post-ganglionic parasympathetic nerve receptors.[viii] These receptors are located in nerves controlling the smooth muscle and the cardiovascular system. Unlike other anti-muscarinic substances, glycopyrrolate does not readily cross the blood/brain barrier – most likely due to its quaternary structure.

When used judiciously, glycopyrrolate can be beneficial to the horse. However, glycopyrrolate has several reported adverse side effects.[ix] In one study, of the 8 horses administered 0.0025 mg/kg of glycopyrrolate, horses experienced side effects including:

- decreased gastrointestinal sounds (6/8)
- mydriasis for 2 days (1/8); and/or
- grade 2 transient heart murmur (3/8)

Administration Study

Intravenous (IV) Administration to Thoroughbred Horses

Glycopyrrolate as a sterile aqueous suspension of 1 mg glycopyrronium bromide (American Regent, Inc.) was administered to twenty exercise-conditioned Thoroughbred horses (geldings and mares). Each horse received a single 1 mg dose in the right jugular vein via direct venipuncture. This administration 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: 0.083, 0.167, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 24, 48, 72, 96 and 168 hours.

Extraction and Analysis Procedures

Quantification of glycopyrrolate in plasma and urine samples was performed at the University of Florida (Gainesville, FL) using validated methods similar to those previously described.[x] Glycopyrrolate was determined in plasma by ultra-high-performance liquid chromatography-mass spectrometry (LC-MS/MS) with heated electrospray ionization-tandem mass spectrometry using a deuterated analogue of glycopyrrolate as internal standard to improve quantitative accuracy and precision. The Limit of Quantification (LOQ) for determination of glycopyrrolate in plasma was 0.125 pg/mL.

Pharmacokinetic Modelling

Plasma concentrations of glycopyrrolate are expressed as the median and range at select collection points (Tables 1.1, 1.2, 1.3, and 1.4). Pharmacokinetic analysis was performed on the intravenous Thoroughbred administration plasma sample concentrations using Phoenix® WinNonlin® pharmacokinetic analysis software (Pharsight Corporation, St. Louis, MO).

Results and Discussion

Following a single intravenous administration of glycopyrrolate, plasma concentration increased rapidly and peak plasma concentrations were achieved soon after IV administration.

Mean (plus standard deviation), median and range of the plasma concentrations for Thoroughbreds after IV administration are shown in Table 1.1.

Table 1.1 Plasma glycopyrrolate mean(±SD) and median values at 24 and 48-hours following intravenous administration of a single dose of 1 mg of glycopyrronium bromide to 20 Thoroughbred horses

Time (hours)	Mean (±SD) (ng/mL)	Median (Range) (ng/mL)
24	1.37 (0.40)	1.24 (0.74-2.25)
48	0.62 (0.26)	0.56 (0.25-1.21)

Scientific Advisory Committee (SAC) Recommendation

In order to ensure that intravenous injections were performed outside of 48 hours prior to racing, the 95/95 Tolerance interval calculation was performed on the 48-hour, log-transformed data resulting in a value of 2.15 pg/mL. This concentration was rounded up by the SAC to a threshold recommendation of 3 pg/mL of glycopyrrolate in plasma/blood corresponding to a single IV dose of 1 mg.

Practice Tips

A later administration study using the same dose (1 mg) and route of administration (IV) was performed at the University of Florida on 6 standardbred horses. 1/6 horses had a plasma concentration of glycopyrrolate in excess of the threshold at 48 hours. The cause for the difference between the values of the two studies was not investigated. In an abundance of caution, veterinarians administering glycopyrrolate to standardbred horses are advised to use a withdrawal interval greater than 48 hours.

The withdrawal guide recommendation of 48 hours is based upon a 1 mg dose of glycopyrrolate as glycopyrronium bromide intravenously. Different formulations of glycopyrrolate, administration of higher doses, use of other routes of administration, or combinations of glycopyrrolate with other substances 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.

References

[i] Rumpler, M.J., *et al., Pharmacokinetics of Glycopyrrolate Following Intravenous Administration in the Horse*, J. vet Pharmacol. Therap. (2011) 34(6): 605-8, *see also*, Plumb, Donald C. "Glycopyrrolate." Plumb's Veterinary Drug Handbook. 8th ed. Stockholm, WI: PharmaVet, 2008. 679-82.

[ii] Rumpler, M.J., *et al.,* J. vet Pharmacol. Therap, 2011., Rumpler, M.J., *et al.*, *Regulatory Control of Glycopyrrolate in Performance horses Using Validated UHPLC/MS-MS Methods*, (2012) Journal of Chromatography B, 889-890: 130-137.

[iii] Rumpler, M.J., *et al.,* J. vet Pharmacol. Therap, 2011. *see also*, Plumb, Donald C. "Glycopyrrolate." Plumb's Veterinary Drug Handbook. 8th ed. Stockholm, WI: PharmaVet, 2008. 679-82, Westermann, C.M., *et al.*, *Effects of Antitussive Agents Administered Before Bronchoalveolar Lavage in Horses*, AJVR, (2005) 66(8): 1420-24, Kutscha, J., *et al.*, *Equine Piroplasmosis Treatment Protocols: Specific Effect on Orocaecal Transit Time as Measured by the Lactose ^{13}C-ureide Breath Test*, Equine Vet Journal Supp., (2012) 43: 62-67.

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

[v] FDA Green Book.

[vi] FDA Green Book.

[vii] FDA Orange Book. https://www.accessdata.fda.gov/scripts/cder/ob (Enter glycopyrrolate in search box)

[viii] Plumb, Donald C. “Atropine” and "Glycopyrrolate." Plumb's Veterinary Drug Handbook. 8th ed. Stockholm, WI: PharmaVet, 2008. 126-130; 679-82.

[ix] Westermann, C.M., *et al.*, *Effects of Antitussive Agents Administered Before Bronchoalveolar Lavage in Horses*, AJVR, (2005) 66(8): 1420-24.

[x] Rumpler, M.J., *et al.*, *Validation of a Liquid Chromatography-Tandem Mass Spectrometry Method for Quantification of Glycopyrrolate in Horse Plasma*, Journal of Analytical Tox., (2011) 35: 656-64.