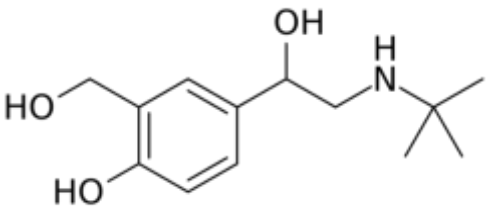
CONTROLLED THERAPEUTIC MEDICATIONS

MONOGRAPH SERIES

Albuterol

Background

Albuterol is a relatively selective β_2-adrenoreceptor agonist with a rapid onset and short duration of action.[i] It is assigned 3/B Classification in the ARCI's Uniform Classification of Foreign Substances, however is associated with a Class A penalty in Quarter Horse racing due to continued abuse. Albuterol is indicated for the relief of bronchospasm and bronchoconstriction in horses with equine asthma and is effective for up to 7 hours as a bronchodilator.[ii] Albuterol is synonymous with salbutamol; albuterol is the nomenclature used in the US while salbutamol is used internationally.



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Albuterol is a prescription medication and can only be dispensed by, upon the request of, a licensed veterinarian.[iii] Albuterol sulfate is FDA approved for use in horses by intranasal administration only.[iv] It was commercially available for horses as Torpex™ [v] and was administered by inhaler in 120 microgram puffs (or actuations) – with doses ranging from 1 to 6 puffs every 6 hours.[vi] The duration of action ranges from a minimum of 1 hour up to 7 hours.[vii] Torpex™ has been withdrawn by the manufacturer, but extra-label use of FDA-approved human inhalation products remains a treatment option. Additionally, tablet, syrup and nebulizing formulations are FDA approved and available for use in humans.[viii] Albuterol is reported to have poorly bioavailability in horses, owing to significant first-pass metabolism effort. The parent albuterol is rapidly metabolized in the liver and excreted in conjugated form, resulting in very low circulating plasma concentrations of unconjugated albuterol.[ix]

Albuterol is a short acting β-agonist.[x] It works at β_2 receptors to relax smooth muscle in the vasculature and bronchi.[xi] Inhaled versions of these substances have the highest efficacy in treating acute bronchospasm.[xii] There is contradictory published research with respect to the potential for performance enhancing effects with albuterol administration.[xiii, xiv, xv]

As with other medications in this class, however, continuous use of albuterol can cause desensitization of the β_2 receptors.[xvi] This results in a decreased efficacy of albuterol for treatment of bronchospasm if used long term, also known as tachyphylaxis.

Administration Studies

Several administration studies have been performed using albuterol sulfate in aerosolized intra-nasal or oral formulations. The doses and laboratory methodologies in these studies varied significantly.

One of the earliest studies was performed to determine the sensitivity of a β_2 agonist/antagonist enzyme-linked immunoassay (ELISA) kit for the detection of albuterol.[xvii] In this study, six horses received individual intranasal doses of 120, 360, and 720 micrograms of albuterol once and then 720 micrograms four times per day for 5 days.[xviii] The ELISA kit sensitivity in this study had a limit of detection (LOD) of 2.7 ng/mL in urine. This ELISA was unable to detect albuterol in urine collected 24 hours after any of the dosing regimens, even after the final administration of the multi-dose study.[xix]

A second study was performed at the University of Florida using both intra-nasal and oral albuterol.[xx] Sixteen exercise-conditioned Thoroughbred horses were administered albuterol. Eight of the horses received 900 micrograms of intra-nasal albuterol sulphate. The other nine horses received 40 mg of albuterol sulfate orally in a syrup form. Urine samples were collected by free catch at 1, 2, 4, 6, 12, 24, 36, and 48 hours for the intra-nasal study and at 2, 4, 6, 8, 12,24, 48, and 72 hours for the oral study. The researchers used an ELISA kit with a LOD of 2.7 ng/mL in urine. Based upon the results, no horse had a detectable level of albuterol at 36 hours after intra-nasal administration. Conversely, not all of the horses receiving the oral dose of albuterol were below 2.7 ng/mL of urine at 48 hours post administration time. These horses were, however, below the 2.7 ng/mL LOD at 72 hours. This has been previously documented for fluticasone and underscores the amount of variability that can exist for these products[xxi].

A third study performed at the Maddy Equine Analytical Pharmacology Laboratory, University of California - Davis investigated yet another dose of albuterol via different methodology[xxii]. In this study, the investigators performed intra-nasal administrations of 360 micrograms plus an additional 120 micrograms of albuterol to 6 exercise-conditioned Thoroughbred horses. Urine samples were collected hourly for 1-6 hours post-administration. The samples were analyzed using LC-MS/MS methodology and the lower limit of quantification (LOQ) was 0.1 ng/mL of urine. At 6 hours, the average urinary concentration of albuterol in these 6 horses was 1.5±0.9 ng/mL of urine.

In a fourth study, researchers administered a single 2000 microgram inhaled dose of salbutamol as Ventolin™ to four untrained Standardbred mares.[xxiii] Urine samples were collected during the first twelve hours and then at 24- and 48-hours post administration. The samples were screened using ELISA kits and confirmed with GC-MS/MS. The LOD for the GC-MS/MS methodology was 0.25 ng/mL of urine. Albuterol could be detected in the urine of each of the horses at 24 hours.

At 48 hours, albuterol could only be detected in the urine of one of the four horses at a concentration of approximately 0.25 ng/mL.

The final study reviewed by the RMTC SAC is a study performed by the European Horseracing Scientific Liaison Committee (EHSLC). The information was shared through a confidentiality agreement with the RMTC SAC. The study involved 6 horses that were administered 500 micrograms of salbutamol via metered dose inhaler every four hours for two days. Urine was collected following administration beyond 72 hours. The samples were analyzed using LC-MS/MS methodology. At 72 hours the concentration of albuterol was well below 1 ng/mL in urine for all 6 horses, the threshold currently in place in the US.

Extraction and Analysis Procedures

Albuterol in the urine is conjugated to sulfonate and glucuronate. Enzyme hydrolysis of the urine removes these from albuterol. Albuterol is extracted from the hydrolyzed urine using solid phase extraction. Analysis of the extracts has been performed successfully using GC/MS/MS [xix] and LC/MS/MS as described above. [xviii] Both methods of analysis are satisfactory to support enforcement of the 1ng/mL threshold.

RMTC Recommendation

The RMTC calculated a 95/95 tolerance interval using data from urine samples collected 6 horses at 72 hours following intra-nasal administration. This calculation generated a value of 0.246 ng/mL and the SAC voted to round that number up to a threshold of 1.0 ng/mL in urine for albuterol with an associated withdrawal time of 72 hours. The recommendation is limited to doses of 720 micrograms or less administered intra-nasally up to four times per day.

Practice Tips

IMPORTANT NOTE: The recommended threshold and withdrawal guidance do NOT apply to Quarter Horse Racing where albuterol is a prohibited substance in recognition of its use as an alternative to clenbuterol for the purpose of increasing lean muscle mass. The use of albuterol in Quarter Horses is controlled with hair testing. Albuterol can be detected in hair for several months after intra-nasal or intravenous administrations.[xxiv]

It is important to note that different formulations of albuterol, administration of higher doses, more frequent doses, different routes of administration, or combinations of albuterol with other substances may 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.

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