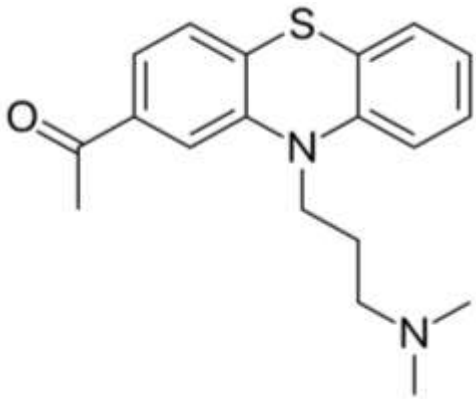
CONTROLLED THERAPEUTIC MEDICATIONS

MONOGRAPH SERIES

Acepromazine

Background

Acepromazine is a phenothiazine derivative widely used in equine veterinary medicine for mild sedation.[i] It is assigned a 3/B classification by the ARCI. Acepromazine can also be used as part of a pre-anesthetic protocol for surgical procedures. Acepromazine is a prescription medication and can only be dispensed from, or upon the request of, a veterinarian. Common trade names for acepromazine include AceproJect™ and PromAce™. Generic versions are also available. It is commercially available in injectable (intravenous and intramuscular) and tablet formulations. Historically, acepromazine was not recommended for use in intact stallions due to risk of prolonged penile prolapse. However, the most recent data suggest this risk is quite low, and many anesthesiologists use this as a pre-anesthetic medication, even in intact stallions.[ii]



"Acepromazine structure" by Emeldir (talk) - Own work. Licensed under Public Domain via Commons - https://commons.wikimedia.org/wiki/File:Acepromazine_200.svg

Acepromazine's specific mechanism of action is poorly understood. Proposed mechanisms include central depression through dopaminergic pathways and peripheral actions including action on cholinergic, histaminergic, and adrenergic receptors.

Administration Studies

Intravenous Administration – Therapeutic Dose

Acepromazine (Acepromazine, generic 10 mg/mL solution from Webster Pharmacy) was administered to twenty exercise-conditioned Thoroughbred horses (geldings and mares) housed at the University of Florida Equine Pharmacokinetics Laboratory. Each horse received a one-time 0.05 mg/kg dose via intravenous injection.

Blood samples were obtained immediately prior to medication administration and at the following times: 5, 10, 15, 20, 30, and 45 minutes; and 1, 2, 3, 4, 6, 8, 24, and 48 hours post-administration. Urine samples were collected immediately prior to medication administration and at 2, 8, 24, 48, 72, 96, and 120 hours post-administration.

Intravenous Administration – Race Day Dose

A "hub" dose, a one-time intravenous injection of 2 mg, was administered to 6 exercised Thoroughbred horses (geldings and mares) housed at the University of California, Davis. The purpose of this dose was to investigate if a low-dose race day administration could be detected.

Blood samples were obtained immediately prior to medication administration and at the following times: 5, 10, 15, 20, 30, and 45 minutes; and 1, 2, 3, 4, 6, 8, 24, and 48 hours post-administration. Urine samples were collected immediately prior to medication administration and at 2, 4, 6, 8, 24, and 48 hours post-administration.

Other published studies have also examined plasma and urine samples after intravenous administration at a 25-30 mg/horse (approximately 0.05 mg/kg) and a much higher dose (0.15mg/kg).[iii,iv,v] Intramuscular administration has also been examined at 25 mg/horse as a single dose or 5 daily 5mg doses.[vi,vii] Finally, oral administration of a gel formulation at 0.5mg/kg or 0.8mg/kg was examined.[viii]

Extraction and Analysis Procedures

Turbulent flow chromatography extraction followed by liquid chromatographic-mass spectral (LC-MS) analysis was used to quantitate acepromazine and its metabolite 2-(1-hydroxyethyl) promazine sulfoxide (HEPS) using stable isotope labeled analogues of the analytes as internal standards. The lower limit of detection for the HEPS in plasma was 5.0 pg/mL and the lower Limit of Quantitation (LOQ) was 10 pg/mL.

Previous studies relied on either LC-MS technology or Enzyme Linked Immunosorbent Assay (ELISA) for quantitation of acepromazine. The LOQ for previously reported LC-MS data is several orders of magnitude higher than the current report as the technology has improved over time. The ELISA has an intermediate limit of quantitation at 82 pg/mL in plasma and 556 pg/mL in urine.

At this time only LC-MS technology has been described for the quantitation of the more persistent HEPS metabolite.[ix, x] The LOQ was reported as 1 ng/mL in both studies examining HEPS concentration.

Pharmacokinetic Modeling

Studies involving all three routes of administration (intravenous, intramuscular, and oral) found acepromazine showed a close fit to a two-compartment open model.[xi, xii, xiii] The metabolism of acepromazine to 2-(1-hydroxyethyl) promazine sulfoxide (HEPS) is rapid and prevents accurate modeling of the distribution of HEPS in the body with currently available data. However, the HEPS elimination phase is approximated with a linear one compartment model.

Acepromazine and HEPS Concentrations in Serum

Plasma concentrations of acepromazine and its metabolite (HEPS) for the therapeutic 0.05 mg/kg dose are shown in table 1.1. The plasma acepromazine peaked at 5 minutes and HEPS concentration peaked at 20 minutes; both were undetectable in all horses at 48 hours.

Previous studies found plasma acepromazine concentrations peaked at 5 minutes after intravenous administration of a 30mg/horse dose.[xiv] The oral gel formulation showed rapid absorption and good bioavailability. The peak plasma concentration after oral administration of 0.5 mg/kg occurred 24 minutes post administration.[xv] Similarly, a 30-minute peak is reported after intramuscular administration of a 25 mg/horse dose.[xvi]

In contrast to the values reported here Chou et al. found acepromazine detectable through 48 hours in serum after intramuscular administration of 25 mg/horse.[xvii] In this study all horses were below the LOQ for the ELISA by 72 hours. This slightly slower elimination is likely attributable to the change in route of administration. Data on oral administration suggest an even slower rate of elimination (half-life of elimination 6.04 hours vs 2.6 hours for IV administration).[xviii]

Table 1.1 Plasma and urine acepromazine and HEPS concentrations (mean ± SD) at selected time points following IV administration of 0.05 mg/kg of acepromazine in 20 horses

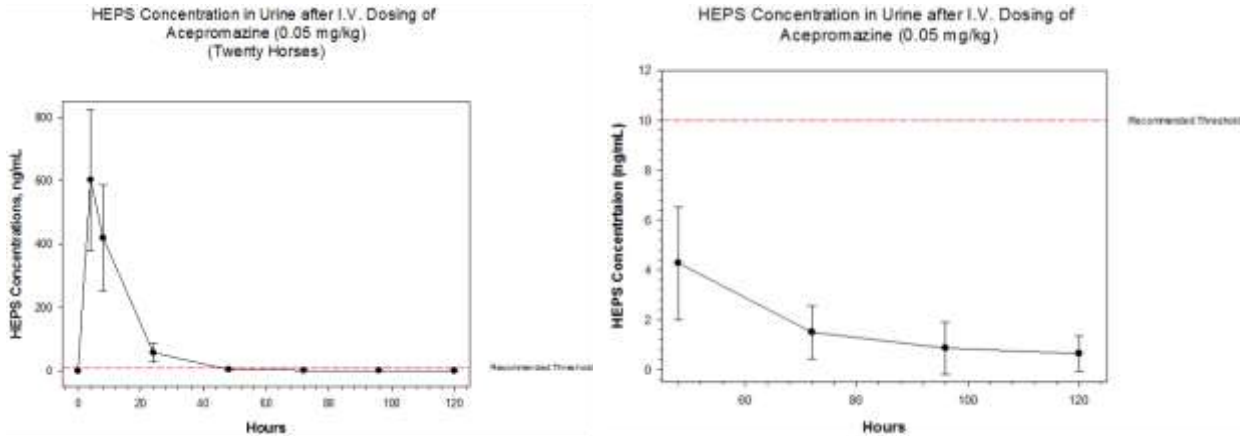
Time	Plasma Ace (ng/mL)	Plasma HEPS (ng/mL)	Urine Ace (ng/mL)	Urine HEPS (ng/mL)
24	0.03±0.00	0.11±0.07	0.454±0.136	57.31±29.45
48	ND	ND	0.364±0.136	4.27±2.26
72	ND	ND	ND	1.5±1.07
96	ND	ND	ND	0.86±1.06
120	ND	ND	ND	0.64±0.72

Acepromazine and HEPS Concentrations in Urine

Urine concentrations of acepromazine and its metabolite 2-(1-hydroxyethyl) promazine sulfoxide (HEPS) for the therapeutic 0.05 mg/kg dose are shown in Table 1.1. Acepromazine in urine peaked at 4 hours and could only be detected in 6/20 horses at 24 hours. HEPS concentration in urine is shown in Figure 1.1. In urine, the HEPS concentration peaked at 4 hours and was detectable in 13/20 horses at 120 hours.

This is consistent with previous reports of acepromazine in urine peaking at 4 hours and decreasing by >80% within 24hrs. Acepromazine was above the LOQ for the ELISA in some horses up to 120 hours after administration of 25 mg via intramuscular injection.[xix]

Figure 1.1 Urine concentrations of HEPS (mean±SD) prior to and following a 0.05 mg/kg acepromazine administration



Scientific Advisory Committee (SAC) Recommendation

Acepromazine's sedative effects have been documented to last at least 6 hours and up to 11 hours post administration depending on the route of administration and dosage .[xx] It is therefore desirable to develop a threshold based on a minimum 48-hour withdrawal interval to ensure there are no residual sedative or hematologic effects of the acepromazine present during competition. Due to its longer half-life and urinary concentration HEPS, the acepromazine metabolite, is the best candidate for detection of acepromazine usage. Neither HEPS nor the parent acepromazine compound are reliably detected in plasma beyond 24 hours; in most cases urine sampling is preferable. Based on the current limits of detection a threshold of 10 ng/ml HEPS in urine is recommended.

The 48-hour withdrawal guidance recommendation for a single 0.05 mg/kg dose of intravenous acepromazine is based on an historical threshold predating the RMTC and supported by data where all study horses' concentrations of HEPS in urine were less than 10 ng/mL at the 48-hour time point. As this predates the RMTC's use of the 95/95 Tolerance Interval calculation individuals may elect to use a longer withdrawal interval to further reduce risk of a concentration in excess of the threshold.

Administrations of higher doses, repeat doses, and other routes of administration, particularly prolonged oral administration 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.

Practice Tips

While acepromazine is also available in compounded formulations, there is risk in using such products in proximity to a race as there have been multiple instances where the concentration of drug in a compounded formulation differs from that declared on the product label. If acepromazine is to be administered in relative proximity to a race, the use of a commercial product represents a potentially safer, more reliable strategy.

Some compounding pharmacies formulate suspensions of acepromazine for oral use. There is risk in using suspensions, even after agitation, as the medication may not be evenly distributed throughout the liquid. This can impact the dose administered as well as the amount of drug in the remaining suspension. Subsequent doses administered may carry concentrations that differ substantially from the product label. Therefore, use of acepromazine suspensions in proximity to a race is not advisable.

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