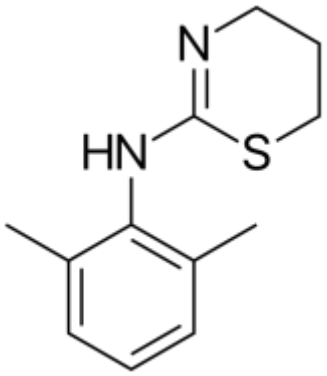
CONTROLLED THERAPEUTIC MEDICATIONS

MONOGRAPH SERIES

Xylazine

Background

Xylazine as xylazine hydrochloride is an alpha-2 adenoreceptor agonist that is commonly used for sedation, analgesia, and muscle relaxation.[i] It is assigned 3/B in the ARCI's Uniform Classification of Foreign Substances. Alpha-2 agonists, like xylazine, are the most commonly used medications for standing procedures.[ii]



https://commons.wikimedia.org/wiki/File:Xylazine.svg

Xylazine is a prescription medication and may only be dispensed from or upon the request of a veterinarian. It is commercially available under the trade name Anased™ and previously under the trade name Rompun™.[iii] Xylazine is most commonly administered intramuscularly and intravenously.[iv] When administered intravenously, it is often combined with other substances such as opiates or local anesthetics.[v] The intravenous and intramuscular doses range from 1.1 milligrams per kilogram intravenously to 2.2 milligrams per kilogram intramuscularly.[vi]

In addition to sedative effects, research has shown a number of additional effects associated with the administration of xylazine. These include:

- Bradycardia, increased AV block, and decreased respiratory rate;[vii]
- Increased rectal temperature;[viii]
- Dose dependent ataxia;[ix] and
- Increased indirect arterial pressure.[x]

Alpha-2 agonists are necessary tools in safe and ethical veterinary practice and horse husbandry. However, use of these products in proximity to a race has the potential to impact a horse's performance and potentially increase risk of racing injury or accident.

There are multiple drug interactions that practitioners should be aware when prescribing or administering xylazine. The following medications are among those that are either associated with adverse reactions when administered in conjunction with xylazine:

- Acepromazine – may cause profound hypotension[xi];
- Epinephrine – ventricular arrhythmias[xii]; and
- Reserpine – a single case study displaying signs of colic.[xiii]

In 2013, the RMTC's Scientific Advisory Committee was asked to approve an interim threshold for xylazine of 0.010 ng/mL in serum with withdrawal guidance of 48 hours and no associated dosing specifications. This was a long-standing historical threshold (and withdrawal guidance) in a racing jurisdiction. The laboratory director advised that there were very few findings reported for xylazine, thus supporting good agreement between threshold and withdrawal guidance. In the absence of administration study data, the SAC approved the historical threshold pending the results of an administration study or availability of new data.

Administration Study

Xylazine hydrochloride as AnaSed™ was administered in a single 200 mg dose to 16 exercise-conditioned Thoroughbred mares and geldings. The administration was performed through a 14-gauge catheter in the jugular vein. Blood collections were performed through another 14-gauge catheter in the contralateral jugular vein.

Blood samples were obtained immediately before dose administration and at the following times after dosing .08, .16, .25, .5, .75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72, and 96 hours post-administration.

Urine samples were also collected at 24, 48, 72, and 96 hours post-administration.

Extraction and Analysis Procedures

Quantification of xylazine in serum was performed at the Maddy Equine Analytical Pharmacology Laboratory at the University of California - Davis, using validated methods described in the publication of this research.[xiv] Xylazine was determined in serum by liquid chromatography-mass spectrometry (LC-MS/MS) using an internal standard for d6-xylazine purchased from Sigma Aldrich to verify quantitative accuracy and precision.

The LC-MS/MS method for determination of xylazine in serum was characterized by a limit of quantification (LOQ) of 10 pg/mL and a limit of detection of (LOD) 5 pg/mL.

Pharmacokinetic Modelling

Xylazine was determined to best fit a three-compartment model of elimination.[xv] Nonlinear least square regression was performed on serum xylazine concentrations using WinNonlin Version 6.2; Pharsight, Cary. The 95/95 tolerance interval was calculated on the natural

logarithmic (*i.e.,* ln) transformed plasma concentration data for all sixteen horses at the 48-hour collection time point after a single 200 mg intravenous dose of xylazine.

Results and Discussion

Xylazine concentrations remained above the LOQ in the majority of horses at 48 hours and were still quantifiable in one horse at 96 hours.

Serum concentrations of xylazine are expressed as the mean, median, and range at 48- and 72-hours post-administration (Table 1.1).

Table 1.1 Serum xylazine mean ±SD, median, and range values at 48- and 72-hours post intravenous administration of 200 mg of xylazine hydrochloride to 16 horses

Time (hours)	Mean±SD (ng/mL)	Median (ng/mL)	Range (ng/mL)
48	0.03±0.01	0.03	0.005-0.05
72	0.01±0.01	0.008	0.005-0.03

Scientific Advisory Committee Recommendation

The RMTC Scientific Advisory Committee rounded up the 95/95 Tolerance Interval calculated value of 115 pg/mL and recommended a regulatory threshold of 200 pg/mL of serum or plasma of xylazine and withdrawal guidance of 48 hours for a single 200 mg intravenous dose.

Practice Tips

The threshold and withdrawal guidance are specific to dose and route of administration. Use of alternate routes of administration (e.g. intramuscular), higher doses, co-administration of other medications 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 the dose and route that were studied and to use an extended withdrawal time and/or submit a sample for analysis prior to competition. Consideration should be given to the horse's condition that required the administration of xylazine, which independent of the medication itself may warrant a treatment-to-race-interval of greater than 48 hours.

References

[i] Lopez-Sanroman, F.J., *et al.*, *Gait Analysis Using 3D Accelerometry in Horses Sedated with Xylazine,* The Veterinary Journal, 2012; 193:212-16.

[ii] Fernandes de Souza, J.F., *et al.*, *Evaluation of Nociception, Sedation, and Cardiorespiratory Effects of a Constant Rate Infusion of Xylazine Alone or in Combination with Lidocaine in Horses*, Journal Equine Vet Science, 2012; 32: 339-45.

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

[iv] FDA Green Book.

[v] Fernandes de Souza, J.F., *et al.*, Journal Equine Vet Science, 2012.

[vi] Plumb, Donald. "Xylazine." Plumb's Veterinary Drug Handbook. 8th ed. Stockholm: PharmaVet, 2015. 1498-1505.

[vii] Fernandes de Souza, J.F., *et al.*, Journal Equine Vet Science ,2012.

[viii] Seo, J.P., *et al.*, *Sedative and Analgesic Effects of Intravenous Xylazine and Tramadol on Horses*, J. Vet. Sci. 2011; 12(3): 281-86.

[ix] Fernandes de Souza, J.F., *et al.*, Journal Equine Vet Science ,2012.

[x] Fernandes de Souza, J.F., *et al.*, Journal Equine Vet Science ,2012.

[xi] Plumb, Donald, 2015.

[xii] Plumb, Donald, 2015.

[xiii] Plumb, Donald, 2015.

[xiv] Knych, H.K., *et al.*, *Pharmacokinetics and Pharmacodynamics of Xylazine Administered to Exercised Thoroughbreds,* Drug Testing and Analysis, 2017 May; 9 (5):713-720.

[xv] Knych, H.K., Drug Testing and Analysis, 2017.