

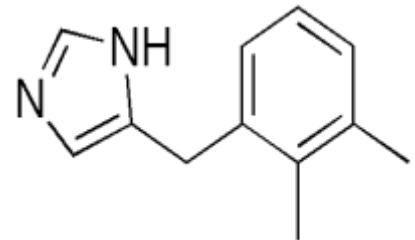


Detomidine

Background

Detomidine as detomidine hydrochloride is an α_2 adrenoceptor 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. Detomidine is typically used to achieve patient restraint during procedures or post-injury.ⁱⁱ

Detomidine is a prescription medication and only dispensed from or upon the request of a veterinarian. It is commercially available under the trade name Dormosedan™.ⁱⁱⁱ Detomidine can be administered intramuscularly, intravenously, and sublingually.^{iv} When administered intravenously, it may be combined with other substances such as butorphanol.^v The intravenous and intramuscular doses range from 0.01 to 0.04 milligrams per kilogram.^{vi} The recommended sublingual dose for horses is 0.04 milligrams per kilogram.^{vii}



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In addition to sedative effects, research has identified additional effects associated with the administration of detomidine including:

- Antipyresis in febrile horses lasting up to 25 minutes post administration;^{viii}
- Increased respiratory rate for more than 5 minutes post administration;^{ix}
- Significant heart-related effects including bradycardia, AV-block, SA-block, with a transient hypertension followed by hypotension;^x and
- Impairment of left arytenoid cartilage abduction during endoscopic evaluation.^{xi}

α_2 agonists are valuable tools in equine veterinary practice. However, their use in proximity to a race can compromise to the integrity of the competition. Accordingly, a threshold and corresponding withdrawal guidance are necessary to ensure that administration of these substances does not impact a horse's racing performance.

In 2013, the RMTC recommended an interim urine threshold of 1 ng/mL of carboxydetomidine, a unique metabolite of detomidine, corresponding to a 72-hour withdrawal recommendation. This recommendation was based on a 2012 pharmacokinetic study for sublingual

administration of detomidine in 12 Dutch Warmbloods.^{xii} The Interim designation was assigned pending the results of scheduled RMTC administration studies.

Administration Studies

IV Administration Study

The RMTC performed a detomidine administration to twenty exercise-conditioned Thoroughbred horses (geldings and mares). Each horse received a single intravenous dose of 0.01 mg/kg of detomidine as Dormosedan™ (Zoetis, Parsippany, NJ). The dose reflected that recommended by the American Association of Equine Practitioners Racing Committee. This study 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 for six of the twenty horses: 0.08, 0.16, 0.25, 0.033, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 24, 48, 72, 96, and 120 hours. The remaining horses were sampled before administration and at 4, 8, 24, 48, 72, 96, and 120 hours after administration.

Urine samples were collected on all twenty horses via free-catch prior to administration and at 4, 8, 24, 48, 72, 96, and 120 hours after administration.

2 mg 'Hub dose' IV Administration Study

A "hub" dose, a one-time intravenous injection of 2 mg, was administered to 9 exercised Thoroughbred horses (geldings and mares) at Kentucky Equine Research (Versailles, Kentucky). The purpose of this administration was to determine if a low-dose race day administration could be detected.

Blood samples were collected at 0, 1, 2, 4, 6, 8, 12, 24, 36, and 48 hours post-administration.

Extraction and Analysis Procedures

Samples from the IV (0.01 mg/kg) were analyzed at the Maddy Equine Analytical Pharmacology Laboratory at the University of California-Davis using liquid chromatography-tandem mass spectrometry (LC-MS/MS) by previously described methods.^{xiii} Internal reference standards for detomidine (Sigma Aldrich, St. Louis, MO) and carboxydetomidine-d4 (Frontier Biopharm, London, KY) were used to verify precision and accuracy. The LC-MS method for determination of detomidine in plasma was characterized by a Limit of Quantification (LOQ) of 0.05 ng/mL and a Limit of Detection (LOD) of 0.025 ng/mL. The LOQ for the validated method for carboxydetomidine in urine was 0.1 ng/mL and the LOD was approximately 0.05 ng/ml.

Samples from the RMTC hub dose were analyzed at LGC Sport Science (Lexington, KY) using internally validated methods by liquid chromatography-tandem mass spectrometry. The LC-MS/MS method for determination of detomidine in plasma was characterized by a LOQ of 5 pg/mL.

Pharmacokinetic Modelling

For the RMTC IV study (0.01 mg/kg) urine carboxydetomidine concentrations are expressed as the mean \pm standard deviation, median, and range at various collection points (Table 1.1). Pharmacokinetic analysis was performed on individual plasma concentrations using Phoenix® WinNonlin® Version 6.2 pharmacokinetic analysis software (Pharsight Corporation, Cary, NC). The 95/95 tolerance interval was calculated on the natural logarithmic (*i.e.*, ln) transformed plasma concentration data at each collection time for all horses. The 95/95 Tolerance Interval calculation was performed on the log-transformed urine data at the 48-hour collection point.

For the RMTC hub dose study (2 mg), plasma detomidine concentrations are expressed as mean \pm standard deviation, median, and range at various collection points (Table 2.1). Pharmacokinetic analysis was performed on individual plasma concentrations using Phoenix® WinNonlin® pharmacokinetic analysis software (Pharsight Corporation, Cary, NC).

Results and Discussion

For the 0.01 mg/kg IV dose administration study, plasma detomidine concentration increased rapidly and peak plasma concentrations were achieved within minutes of IV administration. Plasma detomidine concentrations decreased rapidly and were below LOD for 18/20 at 24 hours and for all 20 horses at 48 hours post-administration.

In urine, the carboxydetomidine concentration peaked 6 hours after intravenous administration. Urine carboxydetomidine concentrations decreased rapidly and were below LOD for all horses by 72 hours post-administration.

Table 1.1 Urine carboxydetomidine mean \pm SD, median and range values at select times following intravenous administration of 0.01 mg/kg of detomidine to 20 horses.

Urine Carboxydetomidine			
Time (hours)	Mean \pm SD (ng/mL)	Median (ng/mL)	Range (ng/ml)
24	16.0 \pm 7.1	16.1	5.4-34.6
48	0.2 \pm 0.3	0.1	0.01-1.0

Table 2.1 Plasma detomidine mean \pm SD, median and range values at select times following intravenous administration of 2 mg of detomidine to 9 horses.

Plasma Detomidine			
Time (hours)	Mean \pm SD (ng/mL)	Median (ng/mL)	Range (ng/ml)
2	0.85 \pm 0.46	0.71	0.49-2.00
4	0.36 \pm 0.19	0.32	0.20-0.81
6	0.20 \pm 0.06	0.19	0.13-0.32

Scientific Advisory Committee (SAC) Recommendation

The SAC determined a urine threshold was required to control the administration of a clinical dose of detomidine to 48 hours. The 95/95 Tolerance Interval calculation yielded a concentration of 1.63 ng/mL which the SAC rounded up to a threshold recommendation of 2.0 ng/mL carboxydetomidine in urine corresponding to a 48-hour withdrawal recommendation for a 5 mg single IV dose. The SAC also determined the need to control for the use of a sub-clinical dose on race day and therefore recommended a plasma threshold of 1.0 ng/mL for detomidine. A violation occurs when either the blood or urine threshold concentration is exceeded.

Practice Tips

The withdrawal guidance is based on the administration of a single intravenous dose of 5 mg of detomidine as Dormosedan. Use of higher doses, different routes of administration, use of compounded products, and/or co-administration with 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 doses and routes that have been studied and to use an extended withdrawal time and/or submit a sample for analysis prior to competition.

There is risk of fatal cardiac arrhythmia when detomidine is administered to horses receiving treatment with potentiated sulfonamides (e.g. sulfamethoxazole/trimethoprim).^{xiv}

There is risk of adverse events when detomidine is administered to horses diagnosed with cardiac arrhythmias or renal failure.^{xv}

When detomidine is to be used as an oral sublingual gel and to determine an appropriate withdrawal interval, it is recommended that veterinarians consult the UC Davis administration study by Dr. H. Knych where 0.04 mg/kg of detomidine gel was administered sublingually to 12 Thoroughbred racing horses.^{xvi}

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^{xv} https://www.zoetisus.com/contact/pages/product_information/msds_pi/pi/dormosedan.pdf

^{xvi} DiMaio Knych, H.K. and Stanley, S.D., *Pharmacokinetics and Pharmacodynamics of Detomidine Following Sublingual Administration to Horses*, AJVR (2011) 72(10): 1378-85.