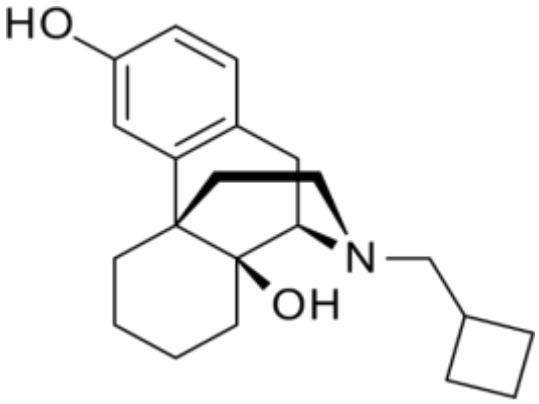
CONTROLLED THERAPEUTIC MEDICATIONS

MONOGRAPH SERIES

Butorphanol

Background

Butorphanol is a mixed opioid agonist-antagonist.[i] It is assigned 3/B in the ARCI Uniform Classification of Foreign Substances. A 2005 study identified it as the main opioid used in equine practice.[ii] It is commonly used in standing surgery, equine dentistry, lameness examinations, and for pain control in colic.[iii] Butorphanol has FDA approval for use in the horse as butorphanol tartrate.[iv] The label approved dose is 0.1 mg/kg by intravenous administration.[v]



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Butorphanol is a prescription medication as well as a DEA Schedule IV substance and can only be dispensed from or upon the request of a veterinarian who holds a DEA license. It is commercially available as butorphanol tartrate and is sold as several FDA approved versions for use in the horse including the trade names Torbugesic™ and Dolorex™.[vi]

Butorphanol works through kappa and sigma opioid receptors in the horse and results in analgesia.[vii] Butorphanol is considered a more potent analgesic than morphine.[viii] Noted adverse effects include cardiovascular effects, ataxia, sedation, and excitement.[ix] Butorphanol undergoes biliary conversion and renal excretion.[x]

Administration Study

Two different butorphanol administration studies were performed. The first was a label dose (0.1 mg/kg, IV) administration study. The second involved “hub” dose administrations of 1 mg or 5 mg of butorphanol. The purpose of the first study was to provide a threshold and withdrawal guidance for label use of butorphanol. The second study was to ensure that the regulation developed would prevent against a low dose administered on race day.

Label Dose Administration Study

A butorphanol administration was performed at the Maddy Equine Analytical Pharmacology Laboratory at University of California-Davis to 10 exercise-conditioned Thoroughbred horses.[xi] Each horse received 0.1 mg/kg of butorphanol as Torbugesic™ intravenously.

Blood samples were obtained immediately before dose administration and at the following times: 5, 10, 15, 20, 30, and 45 minutes post administration as well as 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 18, 24, 36, and 48 hours after administration.

Urinary samples were collected at 24, 48, 72, 96, and 120 hours post-administration.

Hub Dose Administration Study

'Hub' dose administrations were also performed at the Maddy Equine Analytical Pharmacology Laboratory at using 1 mg and 5 mg doses.[xii] For each of these doses, one horse was selected from the original population and received their respective hub dose intravenously.

Following the hub dose administration, blood samples were collected at the following times: 5, 10, 15, 20, 30, and 45 minutes post administration as well as 1, 1.5, 2, 2.5, 3, 3.5, and 4 hours post administration. For the hub administrations study, urine was collected at 1, 2, 3, and 4 hours post administration.

Extraction and Analysis Procedures[xiii]

Plasma Samples

Extraction of butorphanol from plasma was done through turbulent flow chromatography extraction which was followed by LC-MS analysis of butorphanol. Quantitative analysis of plasma samples was completed on a triple quadrupole mass spectrometer paired with a turbulent flow chromatography system. The LC-MS method for determination of butorphanol in plasma was characterized by a Limit of Quantification (LOQ) of 10 pg/mL and a Limit of Detection (LOD) of 5 pg/mL.

Urine Samples

Free and conjugated butorphanol were measured in urine. Following enzyme hydrolysis, samples were analyzed using LC-MS methodology. Quantitative analysis was completed on a triple quadrupole mass spectrometer paired with a turbulent flow chromatography system. The LC-MS method for determination of butorphanol in urine was characterized by an LOQ of 0.1 ng/mL and a LOD of 0.05 ng/mL.

Pharmacokinetic Modelling

Pharmacokinetic analysis was performed on plasma using Phoenix® WinNonlin® pharmacokinetic analysis software (Pharsight Corporation, Cary, NC).

Results and Discussion

Plasma concentrations of free butorphanol peaked quickly after administration. The average half-life was approximately 6 hours. Concentrations of free butorphanol were all below 1.0 ng/ml at 48 hours following intravenous administration of 0.1 mg/kg of butorphanol as shown in Table 1.1.

Limited sampling was done in urine post administration of 0.1 mg/kg intravenously. Concentrations decreased rapidly between 24-and 48-hours post administration. Butorphanol concentrations in samples from eight of the ten horses were below the LOD at 120 hours. Mean, standard deviation, and median of the urine concentrations at 48 hours after the administration of 0.1 mg/kg of butorphanol as Torbugesic™ intravenously are displayed in Table 2.1.

Table 1.1 Plasma concentrations of free butorphanol mean ±SD and median values at 48 hours following IV administration of 0.1 mg/kg of butorphanol tartrate to 10 horses.

Time (hours)	Mean (±SD) (ng/mL)	Median (Range) (ng/mL)
48	0.19 (0.12)	0.18 (0.07-0.45)

Table 2.1 Urine butorphanol mean ±SD and median values at 48 hours following IV administration of 0.1 mg/kg of butorphanol tartrate to 10 horses.

Time (hours)	Mean(±SD) (ng/mL)	Median (Range) (ng/ml)
48	21.9 (±29.3)	12.0 (2.7-99.6)

Following a 0.1 mg/kg dose of butorphanol, the concentration of total butorphanol in urine samples from 2 of the 10 horses was less than 300 ng/mL at 24 hours and less than 300 ng/mL at 48 hours in all study horses. Moreover, all plasma/serum sample concentrations of free butorphanol were less than 2.0 ng/mL at 18 hours post intravenous administration of a 0.1mg/kg dose.

Hub doses of butorphanol of 1 mg and 5 mg on race day yielded concentrations in excess of the urine or plasma thresholds at nearly all time points sampled.

Scientific Advisory Committee (SAC) Recommendation

The RMTC SAC determined that butorphanol should be primarily regulated via a urinary threshold. The 95/95 Tolerance Interval (TI) was calculated on the natural logarithmic (*i.e.,* ln) transformed time data based the concentration of butorphanol at the time point immediately after 48 hours. For plasma, the 95/95 TI was 1.9 ng/mL; for urine, 256.7 ng/mL. The SAC recommended a threshold of 300 ng/ml of total butorphanol in urine to control the use of butorphanol for the 48 hours prior to racing. Additionally, to ensure that a small amount of butorphanol was not administered immediately prior to racing, the RMTC SAC recommended a secondary plasma/serum threshold at 2.0 ng/mL of free butorphanol. This dual threshold is required to control administration of butorphanol on race day as well as within the days before a race. The collection and analysis of paired (blood and urine) post-race samples is necessary to control the use of butorphanol.

Practice Tips

The basis for the threshold and withdrawal guidance was a single intravenous administration of 0.1 mg/kg. Differing doses, formulations, routes of administration, or co-administration with other medications 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

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[iii] Wagner, A.E., *et al.*, *Evaluation of Sedation and Analgesia in Standing Horses After Administration of Xylazine, Butorphanol, and Subanesthetic Doses of Ketamine*, JAVMA (2011), 238(12): 1629-33.

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[v] FDA Green Book.

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

[vii] Plumb, Donald C. "Butorphanol Tartrate." *Plumb's Veterinary Drug Handbook*. 8th ed. Stockholm, WI: PharmaVet, 2015. 182-88.

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[ix] Plumb, Donald C., 2015.

[x] Plumb, Donald C., 2015.

[xi] Knych, H.K., *et al.*, *Pharmacokinetics and Pharmacodynamics of Butorphanol Following Intravenous Administration to the Horse*, J. Vet. Pharmacol. Therap., (2012) 36:21-30.

[xii] Knych, H.K., *et al.*, J. Vet. Pharmacol. Therap., 2012.

[xiii] Knych, H.K., *et al.*, J. Vet. Pharmacol. Therap., 2012.