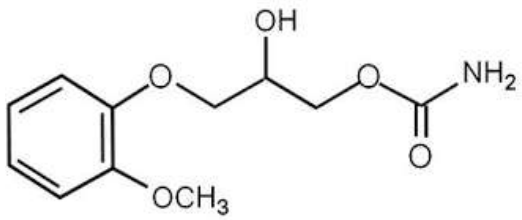
CONTROLLED THERAPEUTIC MEDICATIONS
MONOGRAPH SERIES

Methocarbamol

Background

Methocarbamol (MBCL) is a centrally acting skeletal muscle relaxant that has been used in equine medicine for over 40 years.[i] It is assigned 3/C in the ARCI's Uniform Classification of Foreign Substances. Methocarbamol is labeled for use in horses as "an adjunctive therapy for acute inflammatory and traumatic conditions of the skeletal muscle" as well as "to reduce muscular spasms."[ii] It is used to treat myalgia, dislocations, tetanus, and rhabdomyolysis (tying up).[iii]



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Methocarbamol is a prescription medication and can only be dispensed from or upon the request of a veterinarian. It is commercially available in a variety of oral formulations. An intravenous product with FDA-approval for use in the horse is no longer available; injectable formulations are currently available only through compounding pharmacies. The intravenous dosage of methocarbamol ranges from 4.4 to 55 mg/kg.[iv] A 1992 paper by Cunningham, *et al.*, recommended higher oral doses due to the drug's reduced bioavailability when administered *per os*[v].

The exact mechanism of action for MBCL remains unknown but it is accepted to work as a general depressant that can have sedative effects.[vi] MBCL acts on the interneurons of the spinal cord and produces a preferential block of spinal polysynaptic reflexes decreasing nerve transmission in spinal and supra-spinal polysynaptic pathways.[vii] This could interrupt abnormal impulses from areas of disturbed muscles.[viii]

Methocarbamol is metabolized to guaifenesin (GCE) which is used in veterinary medicine as a skeletal muscle relaxant, expectorant, and pre-anesthetic agent. There are no reports of GCE detection in blood or urine following intravenous MBCL administration. However, the metabolism of MBCL to GCE and the excretion of GCE in urine after oral MBCL administration has been recognized for decades.[ix]

Administration Study

Intravenous (IV) Administration

An compounded formulation of injectable methocarbamol (Wedgewood Pharmacy, Swedesboro, NJ) was administered intravenously at a dosage of 15 mg/kg to twenty adult,

exercise-conditioned Thoroughbred geldings and mares.[x] This study was performed at the University of Florida Veterinary Medical Center (Gainesville, FL) under the direction of Dr. Patrick Colahan.

Blood samples were obtained immediately before dose administration and at the following times after dosing in six of the twenty horses: 5, 10, 15, 20, 30, 45, 60, and 90 minutes and 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours. Collection times for the remaining fourteen horses were: immediately before collection and 24, 48, and 72 hours post-administration.

Oral Administration

Six of the horses that received the intravenous dose were dosed orally with 5 g of generic MBCL after a ten-week washout period. The horses were dosed 5 times at 0, 12, 24, 36, and 48 hours. Each oral dose consisted of ten 500 mg tablets crushed and dispersed in 60 mL of water and delivered via nasogastric tube followed by 60 mL of water to rinse the tube.

Blood samples at the following times after the first dose: 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 48.25, 48.5, 48.75, 49, 49.5, 50, 51, 52, 54, 56, 60, 64, 72, 96, and 120 hours. The samples collected at 12, 24, 36, and 48 hours were collected immediately before the next dose.

Extraction and Analysis Procedures

Quantification of methocarbamol in plasma and urine samples was performed at the University of Florida Racing Laboratory (Gainesville, Florida) using validated methods similar to those previously described.[xi] Methocarbamol was determined in plasma by liquid chromatography-mass spectrometry (LC-MS/MS) using a stable-isotope labelled analogue of methocarbamol as internal standard to improve quantitative accuracy and precision. The Limit of Quantification (LOQ) for determination of methocarbamol in plasma was 1.0 ng/mL and the Limit of Detection (LOD) was 0.5 ng/mL.

Pharmacokinetic Modelling

Pharmacokinetic modeling was performed on methocarbamol plasma concentration vs. time data after intravenous and oral administration using Phoenix® WinNonlin® pharmacokinetic analysis software (Pharsight Corporation, St. Louis, MO). Plasma concentrations of methocarbamol following intravenous (Table 1.1) and oral (Table 1.2) administrations are expressed as the mean, median, and range at the 24- and 48-hour collection points.

Table 1.1 Plasma methocarbamol mean, median, minimum and maximum values following intravenous administration of 15 mg/kg of methocarbamol to 20 horses

Time (hours)	Mean (±SD) (ng/mL)	Median (ng/mL)	Range (ng/mL)
24	4.27 (±3.53)	3.080	2.04-11.21
48	0.23 (±0.13)	0.21	0.06-0.64

Table 1.2 Plasma methocarbamol mean, median, minimum and maximum values following the last oral administration of 5 g of methocarbamol to 6 horses

Time (hours)	Mean (±SD) (ng/mL)	Median (ng/mL)	Range (ng/mL)
24	2.48 (± 1.30)	1.85	1.11-4.70
48	0.24 (± 0.14)	0.22	0.10-.51

Results and Discussion

Following intravenous administration plasma concentrations of MBCL peaked quickly with a mean peak concentration at 5 minutes. At 24 hours post-administration, plasma concentrations were characterized by a median of 3.10 ng/mL with a range of 1.0-13.4 ng/mL. After intravenous administration of MBCL at 15 mg/kg, GCE, the metabolite was not detected in any sample (LOD of 0.5 ng/mL).

Oral administration of MBCL was characterized by a short terminal half-life of 2.89 hours. The bioavailability of MBCL had a median of 54.4 % and a range of 43.2-72.8 %.

By 48 hours after the last oral dose, MBCL concentrations were below the LOQ in all horses studied. After oral administration GCE was quantifiable up to 8 hours and detected up to 16 hours after the last dose.

Scientific Advisory Committee Recommendation

The 95/95 Tolerance Interval (TI) calculation was performed on the 48-hour data from the intravenous administration and resulted in a value of 0.8 ng/mL. In order to control the use of methocarbamol to 48 hours, the SAC recommended rounding up the 95/95 TI value of 0.8 ng/mL to a threshold recommendation of 1.0 ng/mL of methocarbamol in serum or plasma with withdrawal guidance of 48 hours for a single intravenous administration of 15 mg/kg.

Practice Tips

The threshold and corresponding withdrawal guide recommendation are specific to dose (15 mg/kg) and route of administration (IV). Different formulations of methocarbamol, administration methods, administration of higher doses, or combinations of methocarbamol with other substances may result in concentrations above the threshold unless an extended withdrawal time is observed[xii]. Veterinarians are advised to assess the impact of these potential risk factors on the withdrawal time and to advise their clients accordingly.

Specifically, the withdrawal time recommendations do <u>not</u> apply to methocarbamol administered orally because it is cleared more slowly when compared to intravenous administration.

With a half-life of approximately 3 hours methocarbamol would be expected to bioaccumulate with twice daily dosing; longer withdrawal intervals should be used for horses receiving BID treatment.

Additionally, veterinarians should note the possibility of the metabolite guaifenesin being detected in plasma following oral administration of methocarbamol. Co-administration of methocarbamol and guaifenesin may warrant a withdrawal interval greater than 48 hours.

References

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