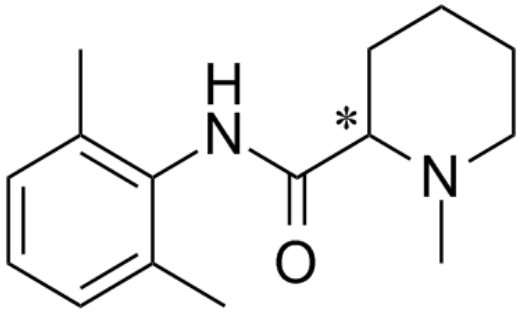
CONTROLLED THERAPEUTIC MEDICATIONS

MONOGRAPH SERIES

# Mepivacaine

## Background

Mepivacaine is a local anesthetic.[i] It is often administered for diagnosis of lameness as a peri-neural or intra-articular anesthetic or as a local anesthetic during procedures such as Caslick's surgery or wound suturing.[ii] It is assigned 2/B in the ARCI's Uniform Classification of Foreign Substances. Mepivacaine has FDA label approval for use in a number of instances with a dose range between 60 mg and 1000 mg of mepivacaine hydrochloride.[iii]

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Mepivacaine is a prescription medication and can only be dispensed from or upon the request of a veterinarian. It is commercially available as mepivacaine hydrochloride and the only FDA approved version for use in the horse is an injectable formulation sold under the trade name Carbocaine™.[iv,v] The FDA approved protocol for mepivacaine varies widely depending on the proposed use.[vi]

Mepivacaine acts via decreasing the speed with which sodium ions are transported into cells.[vii] By doing so, it decreases the ability of the neuron to depolarize. In one study, this effect was shown to last in excess of two hours.[viii] Additionally, when compared with bupivacaine and lidocaine, mepivacaine may have less chondrotoxicity when used in intra-articular anesthesia.[ix]

Mepivacaine undergoes biliary conversion and renal excretion.[x] Its liver metabolism is slower than that of lidocaine.[xi]

## Administration Study

The University of Florida performed an administration of mepivacaine hydrochloride in 5 exercise-conditioned thoroughbred horses. Each horse received 100 mg of mepivacaine hydrochloride as Carbocaine™ subcutaneously (SC) in the distal limb.

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, 2, 3, 4, 6, 8, 24, 48, 72, 96 and 120 hours after administration.

## Extraction and Analysis Procedures

Samples were analyzed at the Iowa State University Veterinary Diagnostic Laboratory. Plasma samples were analyzed by LC-MS/MS. An internal standard, 3-hydroxymepivacaine-d10 (Frontier Biopharm, Richmond, KY) was used to verify precision and accuracy. The method in plasma was characterized by a Limit of Quantitation (LOQ) of 0.1 ng/mL.

The RMTC Scientific Advisory Committee (SAC) reviewed the data and determined that the use of mepivacaine could not be controlled at 72 hours through the analysis of plasma. The SAC reviewed existing information and determined that urine pH is an important factor in the rate of excretion for the parent drug mepivacaine; with lower pH values increasing the excretion rate.[xii] The glucuronidated metabolite concentration, however, is unaffected by pH, thus making a metabolite more suitable for enforcement of regulations.[xiii]

Accordingly, the RMTC contacted the European Horseracing Scientific Liaison Committee (EHSLC) to request urine data from a mepivacaine administration study that it had performed. Those data are subject to a confidentiality agreement between RMTC and the EHSLC. In that study, the EHSLC administered 0.07 mg/kg SC into the distal limb of 6 horses. Urine and plasma were collected at a variety of time points. Urine data from the EHSLC study was used from the first time point at, or after, 72 hours post-administration that urine was collected. Based upon the data collected, the RMTC SAC determined that the metabolite 3 OH-mepivacaine should be used to regulate mepivacaine.

## Pharmacokinetic Modelling

The 95/95 tolerance interval was calculated on the natural logarithmic (*i.e.,* ln) transformed time data based on the urinary concentration of 3 OH-mepivacaine at the time point immediately after 72 hours.

## Results and Discussion

Mepivacaine is rapidly absorbed post administration and has a large volume of distribution. Post administration, it is extensively metabolized via hydroxylation to two metabolites, 3 OH-mepivacaine and 4-hydroxy-mepivacaine. Metabolic clearance is high and these metabolites are rapidly excreted. Both metabolites are excreted in urine as conjugates with glucuronic acid. Various studies have demonstrated peak urine concentrations between 4- and 10-hours post-

administration.[xiv] Peak plasma concentrations occur at approximately 1-hour post-administration (~50 ng/mL) and decrease in a non-linear manner.

In the RMTC study, following a 100 mg SC dose of mepivacaine, concentrations of the parent drug mepivacaine rose rapidly and peaked between 45 minutes and two hours post administration. Concentrations of mepivacaine decreased rapidly after two hours and were below the reported LOQ by 72 hours. Mean plus standard deviation and median of the plasma concentrations after the RMTC's administration of 100 mg of mepivacaine to 5 horses are shown in table 1.1.

**Table 1.1 Plasma mepivacaine mean and median values ±SD at select times following SQ administration of 100 mg mepivacaine hydrochloride to 5 horses.**

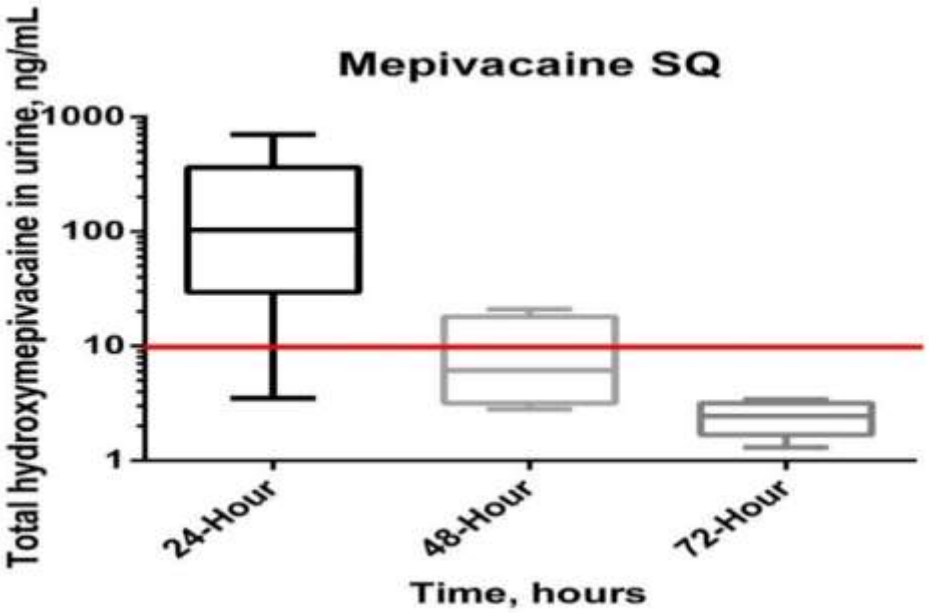
| Time (hours) | Mean±SD (ng/mL) | Median (ng/mL) |
|---|---|---|
| **48** | 0.19±0.33 | 0.02 |
| **72** | 0.01±0.01 | 0.01 |
| **96** | 0.00±0.00 | 0.00 |

Based upon confidential data from the EHSLC, from a 0.07 mg/kg SC administration, concentrations of 3 OH-mepivacaine in urine peaked within 10 hours of administration. Mean plus standard deviation and median of the urine concentrations of 3 OH-mepivacaine at 72-hours after administration of .07mg/kg of mepivacaine to 6 horses are shown in table 1.2.

**Table 1.2 Urine mepivacaine mean and median values ±SD at 72 hours following SQ administration of 0.07 mg/kg mepivacaine hydrochloride to 6 horses.**

| Time (hours) | Mean±SD (ng/ml) | Median (ng/ml) |
|---|---|---|
| **72** | 2.42 ±0.83 | 2.45 |

**Figure 1.1 Urinary concentrations of 3 OH-mepivacaine before and following a 0.07 mg/kg subcutaneous dose.**




## Scientific Advisory Committee (SAC) Recommendation

The 95/95 Tolerance Interval Calculation for 3 OH-mepivacaine in urine at 72 hours resulted in a value of 9.17 ng/mL. The SAC rounded the value up to a threshold recommendation of 10 ng/mL of 3 OH-mepivacaine in urine with corresponding withdrawal guidance for a 0.07 mg/kg dose at 72 hours. Additionally, in order to ensure that a small amount of mepivacaine was not administered immediately prior to racing, the RMTC SAC recommended a secondary plasma/serum threshold at the Limit of Detection. This dual threshold is required to control administration of mepivacaine on race day as well as within the days before a race.

It is important for practitioners to note the dose of 0.07 mg/kg as the basis for the threshold. Increasing the dose, multiple administration sites, different routes of administration (e.g. intra-articular), and co-administration of other medications, all have the potential to change the length of time it would take for urinary and plasma concentrations to fall below the respective thresholds. Additionally, Carbocaine™ was used in each of the experiments. Use of compounded substances could violate federal law and may change the withdrawal requirements.

## References


[i] Katzung, B.G. "Local Anesthetics." *Basic & Clinical Pharmacology*. 10th ed. United States: McGraw-Hill Medical, 2007.

[ii] Katzung, B.G., 2007.

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

[iv] FDA Green Book.

[v] FDA Green Book.

[vi] FDA Green Book.

[vii] Bidwell, L., *et al.*, *Mepivacaine Local Anaesthetic Duration in Equine Palmer Digital Nerve Blocks*, EVJ 2004; 36(8): 723-26.

[viii] Bidwell, L., EVJ, 2004.

[ix] Park, J., *et al*, *Comparison of the Cytotoxic Effects of Bupivacaine, Lidocaine, and Mepivacaine in Equine Articular Chondrocytes*, Vet. Anaesthesia and Analgesia, 2001; 38:127-33.

[x] Katzung, B.G. ,2007.

[xi] Katzung, B.G. ,2007.

[xii] Harkins, *et al., Mepivacaine: Its pharmacological effects and their relationship to analytical findings in the horse*, J. Vet. Pharmacol. Therap. 1999; 22: 107-121.

[xiii] Harkins, *et al.,* J. Vet. Pharmacol., 1999.

[xiv] Harkins, *et al.,* J. Vet. Pharmacol., 1999; *see also* Committee for Veterinary Medicinal Products "Mepivacaine" Summary Report, May 1999, available at: https://www.ema.europa.eu/en/documents/mrl-report/mepivacaine-summary-report-committee-veterinary-medicinal-products_en.pdf