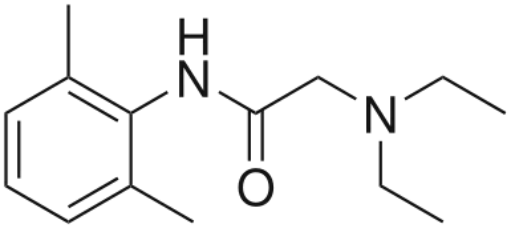
CONTROLLED THERAPEUTIC MEDICATIONS

MONOGRAPH SERIES

Lidocaine

Background

Lidocaine, known as lignocaine outside the US, is an amide local anesthetic often used in the diagnosis of lameness as a peri-neural or intra-articular anesthetic or as a local anesthetic during procedures such as castration surgery or wound repair.[i] Additionally, it is used as an anti-arrhythmic drug, as a treatment for ileus following gastrointestinal surgery, and during surgery as part of the anesthetic protocol.[ii] Lidocaine is assigned 2/B in the ARCI's Uniform Classification of Foreign Substances. It has FDA label approval for use in humans and is a component of FDA approved oxytetracycline products for animals.[iii]



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Lidocaine, as lidocaine hydrochloride, is available in injectable formulation as a prescription medication that can only be dispensed from or by the request of a veterinarian. It is also a constituent of some over-the-counter topical creams, ointments, and patches. In the equine, lidocaine is readily absorbed through mucous membranes and disrupted skin; and to a far lesser extent through intact skin.[iv] There is no FDA approved dosage recommendation for lidocaine in the horse; dosing varies widely.[v]

Lidocaine has multiple modes of action that include decreasing the speed of sodium ion transport into cells thus decreasing the ability of neurons to depolarize.[vi] Generally, this effect is believed to last up to one hour. Lidocaine may have more chondrotoxicity than mepivacaine when used for intra-articular anesthesia, however the results of research are conflicting.[vii]

Administration Study

An administration study of lidocaine hydrochloride using 6 exercise-conditioned Thoroughbred horses was performed at the University of Florida by personnel in the Equine Pharmacokinetics Laboratory under the direction of Dr. Patrick Colahan. Each horse received 200 mg of lidocaine hydrochloride subcutaneously (SQ) over the carpus in one forelimb.

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

Quantification of lidocaine in plasma samples was performed at the University of Iowa Veterinary Diagnostic Laboratory using validated methods. An extraction of 3-hydroxyl-lidocaine was performed in plasma. The plasma extract was analyzed following enzyme hydrolysis by liquid chromatography-mass spectrometry (LC-MS/MS) using 3-hydroxyl-lidocaine-d10 as an internal standard to demonstrate quantitative accuracy and precision. The Limit of Quantification (LOQ) for determination of 3-hydroxyl-lidocaine was 20 pg/mL in plasma.

Pharmacokinetic Modeling

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

The concentrations of 3-hydroxyl-lidocaine in samples were below LOQ for 1 of 6 horses at 24 hours and for all 6 horses by 48 hours.

Results and Discussion

Lidocaine is rapidly absorbed post administration and has a large volume of distribution. It is extensively metabolized via hydroxylation to three metabolites – monoethylglycinexylidide, 3-hydroxyl-lidocaine, and 4-hydroxyl-lidocaine. Metabolic clearance is high and these metabolites are rapidly excreted.[vi]

In plasma, following a 200 mg dose of lidocaine, concentrations of the parent drug rose rapidly and peaked between 30- and 45-minutes post administration. Concentrations of 3-hydroxyl-lidocaine also rose rapidly and peaked between 45 minutes and 2 hours post administration. Plasma concentrations of 3-hydroxyl-lidocaine decreased rapidly after 2 hours and were below the LOQ by 48 hours in all horses. Mean ± standard deviation, median, and range of the plasma concentrations 3-hydroxyl-lidocaine after the SQ administration of 200 mg of lidocaine to 6 horses are shown in Table 1.1.

Table 1.1 Plasma 3-hydroxyl-lidocaine concentration mean ± SD, median, and range at various time points following SQ administration of 200 mg lidocaine hydrochloride to 6 horses.

Time (hours)	Mean±SD (ng/mL)	Median (ng/mL)	Range (ng/ml)
24	0.027± 0.010	0.027	0.013-0.042
48	0.007± 0.002	0.007	0.005-0.10
72	0.004± 0.004	0.003	0.00-0.009

Scientific Advisory Committee (SAC) Recommendation

The RMTC SAC determined that subcutaneous administration of lidocaine could be regulated in plasma using a threshold of 20 pg/mL of 3-hydroxyl-lidocaine. While all samples were below the LOQ at 48 hours, because of the small number of horses in the study, the withdrawal guidance was extended to 72 hours.

The RMTC SAC recommended a regulatory threshold of 20 pg/mL (0.02 ng/mL) of 3-hydroxyl-lidocaine (3-OH lidocaine) in serum or plasma and corresponding withdrawal guidance of 72 hours for a single SQ 200 mg dose.

Practice Tips

Practitioners should note that a single subcutaneous dose of 200 mg was the basis for the threshold. For a 2% lidocaine solution this equates to a total dose of 10 mLs. Increasing the dose or using a different route of administration (e.g., topical) has the potential to change the length of time required for the plasma concentration to fall below the threshold. Lidocaine was the only substance administered to horses during this experiment. The extent to which co-administration of other substances may alter the pharmacokinetic properties of lidocaine is unknown.

References

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[iv] Soma, Lawrence R., *et al., Pharmacokinetics of intravenous, subcutaneous, and topical administration of lidocaine hydrochloride and metabolites 3-hydroxylidocaine, monoethylglycinexylidide, and 4-hydroxylidocaine in horse,* J Vet Pharamcol Ther. 2018; 41(4):825-837.

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[vii] 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; *see also* Piat, P., *et al.*, *In Vivo Effects of a Single Intra-Articular Injection of 2% Lidocaine or 0.5% Bupivacaine on Articular Cartilage of Normal Horses*, Vet Surg., 2012; 41:1002-10.