



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

MEPIVACAINE

SUMMARY REPORT

1. Mepivacaine (N-(2,6-dimethylphenyl)-1-methyl-2-piperidine-carboxamide; synonym: chlorocain, carbocaine), is a racemic tertiary amide local anaesthetic used as its hydrochloride salt in horses for infiltration, peripheral nerve block and epidural and intra-articular anaesthesia (i.e. in the distal interphalangeal joint to alleviate pain in navicular disease). The concentration available for horses is a 2% solution. The common therapeutic doses range from 20 to 160 mg/animal.

In humans, mepivacaine has been used for all types of infiltration and regional nerve-block anaesthesia, as well as for spinal anaesthesia. The dose in humans is up to 7 mg/kg bw. Concentrations of 1% and 2% in combination with 1:200 000 epinephrine are also available.

2. Few specific data on pharmacodynamic properties of mepivacaine were available. Mepivacaine acts on central and autonomic nervous systems, cardiovascular and respiratory systems and gastrointestinal tract. Its mechanism of action is to prevent the generation and conduction of the nerve impulse. Local anaesthetics block conduction by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na⁺ that is produced by a slight depolarization. This action of local anesthetics is due to their direct interaction with voltage-sensitive Na⁺ channels. The pharmacological properties of mepivacaine are similar to those of lidocaine. Its onset of action (11 to 12 minutes) is similar to that of lidocaine and its duration (about 1 hour) is slightly longer (about 20%). Mepivacaine is about twice as potent in producing analgesia as procaine. The available data on pharmacodynamic properties of mepivacaine were insufficient to derive a pharmacological NOEL.
3. Pharmacokinetics of mepivacaine were studied in guinea pigs, rabbits and horses (doses not stated). In the guinea pig, the *d*-isomer of mepivacaine was found to be more rapidly absorbed from the injection site (route not stated) than the *l*-isomer. This effect might be the cause of the significantly longer duration of infiltration anaesthesia by the *l*-isomer than by the *d*-isomer. In the rabbit, after intravenous administration of mepivacaine isomers, significantly greater amounts of the *l*-isomer were found in the lung and kidney. However, greater concentrations of the *d*-isomer were found in the cerebellum, which can explain the observations that *d*-mepivacaine is more toxic than *l*-mepivacaine. Between 77% and 80% of the drug is bound to plasma proteins. Mepivacaine also crosses the placenta. Mepivacaine is slightly less lipid soluble and more highly protein bound than lidocaine.

Plasma concentrations of mepivacaine were determined in adult mares after injection of a 2% solution of mepivacaine hydrochloride (91.4 mg/animal) into either the sacral epidural or the mid-sacral subarachnoidal space. The rate of vascular absorption of mepivacaine from the epidural space was significantly faster than from the subarachnoidal space. Maximum concentrations in plasma were observed between 51 and 55 minutes after administration and were 0.05 µg/ml for both types of injection. After 60 and 75 minutes, mean plasma concentrations were higher for epidural than for subarachnoidal injection: 0.04 µg/ml versus 0.02 µg/ml and 0.03 µg/ml versus 0.02 µg/ml, respectively. Plasma concentrations at cessation of analgesia were not significantly different (0.03 µg/ml versus 0.02 µg/ml). Such concentrations did not produce direct systemic effect on the cardiovascular system of conscious mares.

In Standardbred horses, mepivacaine hydrochloride (30 mg/animal) given by thoracolumbar subarachnoidal injection produced analgesia within 7.5 minutes. Spinal fluid concentrations were 204 µg/ml. Average spinal fluid concentrations at 120 minutes after dosing were 16 µg/ml. The decline of subarachnoidal mepivacaine concentration, which determines the duration of analgesia, was due to absorption of the substance into systemic circulation, not to hydrolysis in spinal fluid.

The distribution of mepivacaine hydrochloride after distal interphalangeal joint injection (8 ml of a 2% solution) was evaluated in 10 horses (several strains). Concentrations in synovial and bone tissue were compared with the estimated effective tissue concentration of mepivacaine for local anaesthesia (0.3 µg/mg). Tissue concentrations of mepivacaine averaged 9.18 µg/mg in distal interphalangeal joint synovia, 3.37 µg/mg in the navicular bursa synovia and 0.41 µg/mg in the navicular bone tissues.

No data on oral bioavailability in laboratory animals were provided.

4. Mepivacaine is extensively metabolised in the rat. About 60% of the dose is excreted in urine as conjugated 3-hydroxymepivacaine. Only trace amounts of the unchanged compound and the N-demethylated metabolite are found in the urine. Oxidation in the *p*-position of the aromatic ring was not observed.

In horses, after subcutaneous administration of 395 µg/kg bw mepivacaine hydrochloride in a 2% solution, urinary excretion of mepivacaine and its main metabolite 4-hydroxymepivacaine occurred over 50 hours and 33 hours respectively, with peak excretion around 6 to 10 hours after administration. There was evidence that 2,6-xylylidine and or 2-pipecoloxylidine are not major metabolites but their production could not be fully excluded.

In humans, mepivacaine is rapidly metabolised in the liver, only about 1% of an oral dose of mepivacaine (50 mg per person) is eliminated unchanged into urine. Similar amounts are found of the N-demethylated metabolite (2-pipecoloxylidine). The major metabolic pathway involves oxidation in the C3- and C4-position of the aromatic ring to yield 3-hydroxy- (20%) and 4-hydroxy-mepivacaine (12%), excreted mainly as glucuronide conjugates. About 10% of the administered dose is recovered as three α -piperidone analogues of mepivacaine. A higher urinary recovery of unchanged mepivacaine (16%) is seen after intravenous administration of 43 mg mepivacaine. The N-demethylated metabolite is also excreted unchanged in urine. Over 50% of a dose is excreted as metabolites into the bile but probably undergoes enterhepatic circulation as only a small amount is excreted in the faeces. Elimination half-life and body clearance in human beings are about 114 minutes and 0.78 l/min respectively.

5. The intravenous LD₅₀ values in mice and rats were 35 to 44 mg/kg bw and 35 mg/kg bw for *dl*-mepivacaine, 34 to 49 mg/kg bw and 37 mg/kg bw for *l*-mepivacaine, and 32 to 40 mg/kg bw and 36 mg/kg bw for *d*-mepivacaine, respectively. In mice, after subcutaneous administration there were differences in the LD₅₀ values for mepivacaine isomers, the *d*-isomer being more toxic (175 mg/kg bw) than the *dl*-mepivacaine (280 mg/kg bw) and the *l*-mepivacaine (330 mg/kg bw). In rats, however, these differences were not of significance (LD₅₀ values: 500 to 530 mg/kg bw).
6. No studies on the repeated dose toxicity of mepivacaine were provided.
7. No tolerance studies in horses were provided. However, no signs of intolerance to mepivacaine were described.
8. No reproductive toxicity including embryotoxicity/foetotoxicity studies were presented. Mepivacaine crosses the placenta, there is, however, no evidence that this compound was associated with reproductive toxicity or teratogenic effects.
9. Studies on potential mutagenic or genotoxic activities were not available.
10. No carcinogenicity studies were provided.
11. No data on immunotoxicity were presented, but mepivacaine has not potential immunotoxicological properties.

12. Published literature on observations in human was available, which contains insufficient data to derive a pharmacological NOEL. The common signs or accidents seen after administration of mepivacaine include at low doses the stimulation of cortical and other cerebral functions (e.g. hyperactivity, hyperreflectivity, tremors). At high doses, there is a progressive ascending depression of functions resulting in sleepiness, stupor, ataxia and eventually loss of consciousness. Nausea and vomiting are sometimes seen after systemic administration. Mepivacaine can also cause vasodilatation and an increase in forearm blood flow. Mepivacaine is more toxic to the neonate and thus is not used in obstetrical anaesthesia. The increased toxicity of mepivacaine in the neonate is not related to a slower metabolism in the neonate, but to ion trapping of this agent because of the lower pH of neonatal blood and the pKa of mepivacaine.

In 5 pregnant women, after caudal epidural injection of mepivacaine hydrochloride solution, signs of toxicity such as apprehension, muscular twitching, and hypotension were reported, associated with a mean mepivacaine plasma concentration of 6.27 µg/ml. In *in vitro* systems mepivacaine was shown to be porphyrinogenic and thus is considered unsafe in patients with acute porphyria.

Information on the oral bioavailability in man was not available.

13. From the available data, neither a pharmacological nor a toxicological NOEL could be identified and thus an ADI cannot be established.
14. No residue studies in food producing animals following administration of mepivacaine at recommended local anaesthetic doses were provided. However, considering the available pharmacokinetic data, it is unlikely that consumers would be exposed to harmful levels of residues of mepivacaine resulting from treatment of food-producing animals.
15. No routine analytical method for the determination of mepivacaine in edible tissues of target animals was presented.

Conclusions and recommendation

Having considered that:

- mepivacaine is used in a small number of individual animals only, for infrequent and non-regular treatments,
- the animals are unlikely to be sent for slaughter during or immediately after treatment,
- mepivacaine is extensively metabolised and rapidly excreted;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for mepivacaine and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Mepivacaine	Equidae	For intra-articular and epidural use as anaesthetic only