COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

LIDOCAINE

SUMMARY REPORT

1. Lidocaine (2-(diethylamino)-N-(2,6-dimethylphenyl) acetamide, synonym: lignocaine), is a water-soluble local anaesthetic. Lidocaine is an aminoethylamide and it is the prototypical member of the amide class of local anaesthetics. It is used as a sterile aqueous solution in cattle, horses, swine, goats and sheep prior to surgery for low and high epidural anaesthesia (cattle), local-regional anaesthesia (horses), epidural and intercostal anaesthesia (swine) and epidural anaesthesia (sheep, goats). Lidocaine is occasionally used intravenously in large animals in the treatment of ventricular arrhythmia. The common therapeutic doses range from 1 to 4 mg/kg bw.

    Lidocaine is also used in human beings for cardiac treatment at usual doses in the range of 3 to 10 mg/kg bw.

2. Lidocaine acts on the central nervous system, cardiovascular system, respiratory tract, digestive tract, striated muscle fibres, urinary and reproductive tract. Lidocaine is a local anaesthetic, 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 depolarisation. This action of local anaesthetics is due to their direct interaction with voltage-sensitive Na^+ channels. Lidocaine produces faster, more intense, longer-lasting, and more extensive anaesthesia than an equal concentration of procaine. The pharmacodynamic data provided were insufficient to derive a pharmacological NOEL.

3. The pharmacokinetics of lidocaine were studied in guinea pigs and dogs. Lidocaine is rapidly and widely distributed regardless of the route of administration. In pregnant guinea pigs administered 10 mg/kg bw of lidocaine (route not stated) it rapidly crossed the placenta. High concentrations were found in the foetal liver, heart and brain. The liver of the foetal guinea pig was the only organ in which concentration of lidocaine was higher than in the maternal subject. In the dog, after oral administration, 78% of the dose reaches the systemic circulation. After intravenous administration of single doses (6 mg/kg bw) the mean elimination rate constant and the mean specific clearance were 0.786 h^{-1} and 2.4 l/kg/h respectively. After intramuscular administration in dogs the mean absorption rate constant was 7.74 h^{-1} and its absorption was essentially complete (91.9%). Lidocaine is metabolised primarily in the liver at a rate nearly as rapid as that for procaine. The unchanged form is excreted in urine in a percentage of 10 to 20%. Two metabolites have been identified in the dog resulting from hepatic N-de-ethylation of lidocaine. One of these, monoethylglycinexylidide, possesses significant pharmacological activity; after a second N-de-ethylation glycinexylidide is formed. Following loss of an ethyl group from its diethyl-amino group, lidocaine is hydrolysed. A large amount of lidocaine is conjugated with sulphate and excreted in this form. In man, 2,6-xylidine and other metabolites have been identified in urine but the percentage is unknown.

In horses, following subcutaneous administration of ^{14}C-lidocaine (200 mg per animal), the percentages excreted in the urine were 0.2% unaltered and 0.4% conjugated lidocaine, 1.5% unaltered and 2.4% conjugated monoethylglycinexylidide, 0.8% unaltered and 0% conjugated glycinexylidide, 0% unaltered and 10.1% conjugated 3-hydroxylidocaine, 0% unaltered and 3.8% conjugated 3-hydroxy-monoethyl-glycinexylidide, 2.5% unaltered and 0% conjugated 2,6-xylidine and 0% unaltered 4-hydroxy-2,6-xylidine, the conjugated form of which was not measured. After 58 hours 77% of the administered radioactivity had been excreted in the urine.

In the urine of other species, 2,6-xylidine accounted for 16.2% in guinea-pigs, 1.6% in dogs, 1.5% in rats, and 1% in man (no further information was available). It has been demonstrated that metabolism and excretion of lidocaine are species-dependent.

In sheep, several pharmacokinetic studies were carried out to determine the difference between pregnant and non-pregnant ewes, suggesting a dose-related distribution of lidocaine after intravenous administration. After intravenous injection of lidocaine hydrochloride at a dose of 4 to 5 mg/kg bw over 60 seconds, pregnant ewes show a greater volume of the central compartment (1.51 l/kg *versus* 0.96 l/kg) and volume of distribution at steady state (3.24 l/kg *versus* 1.88 l/kg) than non-pregnant ewes. There were no significant differences in the elimination half-lives of lidocaine.

No pharmacokinetic studies were submitted for cattle and goats; neither were data on tissue distribution of lidocaine or its metabolites in edible tissues available.

4.   Oral and subcutaneous LD_{50} values in mice ranged between 200 and 400 mg/kg bw while intramuscular LD_{50} values of lidocaine in rats were 260 mg/kg bw.

5.   No studies concerning repeated dose toxicity were provided.

6.   No tolerance studies of lidocaine in target species were provided.

7.   No multigeneration studies in mammalian species were presented.

A study was conducted on male and female rats administered orally 30 mg/kg bw of lidocaine daily for 8 months. During that period, 3 matings were conducted and reproductive parameters were analysed for each gestation, as well as offspring development up to weaning. No effects could be detected.

8.   The teratogenicity of lidocaine was studied in rats after oral and intraperitoneal administration. Female Sprague-Dawley rats aged 9 to 10 weeks, divided into 6 groups (2 controls, 1 positive control group treated with 10 mg retinoic acid/kg bw orally at day 10, 11 and 12 of pregnancy, and 3 groups dosed with 100, 250 and 500 mg/kg bw/day of lidocaine). Control and lidocaine groups received intravenous delivery of physiological saline (control) or lidocaine by means of an osmotic pump two weeks prior to mating and throughout pregnancy, except for the 500 mg/kg bw group, to whom lidocaine was administered on days 3 to 17 of pregnancy. At day 21 of pregnancy the females were sacrificed and their offspring analysed for potential external, visceral or skeletal malformation. No specific teratogenic effect was observed in any of the treated groups. A second study was conducted in 6 to 10 week-old pregnant Sprague-Dawley rats, which received a 4% lidocaine hydrochloride solution intraperitoneally at 56 mg/kg bw, the maximum non-convulsive dose. Lidocaine does not produce any teratogenic effect. A NOEL could not be identified as the studies presented were of inadequate quality.

9.   Genotoxicity studies were carried out with lidocaine and its metabolites. The *Salmonella*-microsomal assay (*Salmonella typhimurium* strains TA100, TA98, and TA1538 with 1, 10, 100 and 500 mg/plate), with or without metabolic activation, with lidocaine and its metabolites mono-ethylglycinexylidine, N-hydroxylidocaine, N-hydroxy-monoethylglycinexylidine, 2,6-xylidine, 2,6-dimethylphenylhydroxylamine, did not reveal any mutagenic activity. However these studies were poorly carried out.

Further mutagenicity tests were carried out with the metabolite 2,6-xylidine, with positive results in the *Salmonella*-microsomal assay (*Salmonella typhimurium* strain TA1538 with 1, 10, 100 and 500 mg/plate) with metabolic activation, causing forward mutation in the mouse lymphoma assay at the tk-locus, chromosome aberration and sister chromatid exchange in Chinese hamster ovary (CHO) cells, the latter two in the presence of precipitated compound. The *in vitro*/*in vivo* test for unscheduled DNA synthesis in rat hepatocytes, tests for covalent binding to DNA in rat liver and ethmoid turbinates *in vivo*, micronuclei in mouse polychromatic erythrocytes and the preferential killing of DNA repair deficient *Escherichia coli* bacteria *in vivo*, using a host-mediated assay in the mouse as well as the *Salmonella*-microsomal assay without metabolic activation were negative. With regard to the covalent binding test it should be noted that it was negative only after treatment with a single dose of ^{14}C-2,6-xylidine, while after a 9-day pretreatment with non-labelled compound the test was positive.

These tests indicated that 2,6-xylidine is a mutagenic agent *in vitro* and has genotoxic characteristics *in vivo*.

10. No studies on carcinogenicity were provided for lidocaine, but a 2-year carcinogenicity study was carried out with 2,6-xylidine in Charles River CD rats administered daily, for 102 weeks, diets containing 0, 15, 50, or 150 mg/kg bw. Over this period both male and female rats of the high dose group showed a noticeable decrease in bodyweight gain (more than 10%). A reduction was also observed in the 50 mg/kg bw group. A significant increase in the incidence of nasal cavity papillomas and carcinomas was observed in high dose males and females. There was a significant dose-related increase in the incidence of adenomas in the nasal cavity of both males and females. In addition, unusual rhabdomyosarcomas and malignant mixed tumours of the nasal cavity were observed in both sexes of the high dose group. A significant dose-related increase in the incidence of subcutaneous fibromas and fibrosarcomas in treated males and females was also seen.

11. No data on the immunotoxicity of lidocaine were presented.

12. Published literature on observations in humans was provided, which contains insufficient data to derive a pharmacological NOEL. The side effects of lidocaine seen with increasing doses include drowsiness, tinnitus, dysgeusia, dizziness, and twitching. As the dose increases, seizures, coma and respiratory depression and arrest will occur. Clinically significant cardiovascular depression usually occurs at serum lidocaine levels that produce marked central nervous system effects. Information on the oral bioavailability in man was also not available.

13. From the available data neither a pharmacological nor a toxicological NOEL could be identified, and thus an ADI cannot be calculated.

14. No residue studies in food producing animals following administration of lidocaine at recommended local anaesthetic doses were presented. However, the available pharmacokinetic data in horses show a rapid metabolism and extensive excretion in this species. In view of the species dependant metabolism no extrapolation on other target species can be made.

Conclusions and recommendation

Having considered that:

- lidocaine 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,
- lidocaine is rapidly metabolised and extensively excreted in horses,
- in absence of adequate metabolism data on animal species other than horses, no recommendation could be made for other target species;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for lidocaine 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
Lidocaine	Equidae	For local-regional anaesthesia only