



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

PENETHAMATE (HYDRIODIDE)

SUMMARY REPORT (1)

1. Penethamate is the diethylaminoethyl ester of benzylpenicillin. In formulations intended for veterinary use the compound is incorporated as the hydriodide. Penethamate is used in intramammary products for treatment of mastitis in cows and as an injectable for treatment of bacterial infections in swine, cattle, horse, goat and sheep.
2. Penethamate is a prodrug from which benzylpenicillin and diethylaminoethanol are released by hydrolysis. Antimicrobial activity of the compound is exclusively related to benzylpenicillin .
3. Penethamate and procaine penicillin have similar profiles with respect to pharmacological properties. Penethamate possesses local anaesthetic activity, an effect also observed with other esters of diethylaminoethanol. In experimental animals rapid intravenous administration gives rise to anticholinergic (atropine-like) and cardiac depressing effects. These effects are not observed in connection with intramuscular injection.
4. Penethamate is a base; at room temperature the pK_a is 8.4. At physiologic pH (7.2) 8 pct of the drug will be present as the uncharged molecule while 92 pct will be in the cationic state.
5. Penethamate is rapidly converted into benzylpenicillin. At 37°C and pH 7.3 (physiological conditions) the half-life of penethamate in aqueous solution is 23 minutes. In tissue homogenate at 32°C half of the penethamate was hydrolysed within two hours and at 20 hours no penethamate remained.
6. Benzylpenicillin itself is of low toxicity. Consequently, the toxic effects of the penicillin esters will depend on the alcohol released by hydrolysis is the determining factor. Since procaine penicillin and penethamate hydriodide both contain an esterified diethylaminoethanol group, which is released by hydrolysis, the two compounds have similar toxicological profiles.
7. In laboratory animals the acute LD_{50} of penethamate hydriodide is greater than or equal to 2000 mg/kg bw following oral or subcutaneous administration, 300-1650 mg/kg following intraperitoneal administration, and 30-90 mg/kg bw in connection with intravenous administration.
8. In repeat-dose toxicity studies subcutaneous administration of 200 mg/kg bw daily for seven weeks to rats did not affect the growth rate or gave rise to significant changes in haematological parameters; nor were any treatment-related abnormalities detected at autopsy at the end of the study period. Similar results were obtained in a study with rabbits administered by intramuscular injection a dose of 25 or 50 mg/kg daily for 20 to 36 days.
9. The acute oral LD_{50} of diethylaminoethanol in rats is 1300-5600 mg/kg. The LD_{50} following intraperitoneal administration is 1220 mg/kg. Like several other aliphatic amines diethylaminoethanol is an ocular and mucous membrane irritant. The small amounts of diethylaminoethanol released by hydrolysis of penethamate make any toxicological risk from this compound appear unlikely.

10. No formal studies have been carried out regarding reproductive toxicity, mutagenic/carcinogenic potential, immunotoxicity, and microbial properties of residues in animals treated with penethamate. Since penethamate is quickly hydrolysed into benzylpenicillin within the body there is little reason to assume penethamate to act significantly different from benzylpenicillin. The effects of benzylpenicillin are well-known.
11. No residue studies were submitted as penethamate is rapidly converted into benzylpenicillin.
12. More than 400 persons have received penethamate hydriodide in studies. From these it appears that the toxicity of penethamate hydriodide is low and comparable to that of procaine penicillin. Penethamate has been authorised for human use in several European countries and in the USA.
13. There is a validated analytical method for the detection of benzylpenicillin in edible bovine tissues and milk. Its limit of quantification is 3 µg/l for milk and 10 µg/kg for edible tissues. Its limit of detection is 0.9 µg/l for milk and less than 2 µg/kg for edible tissues.

Conclusion and recommendation

Considering that:

- Σ Penethamate is a β-lactam antibiotic which has been used in food-producing animals for decades and is thus a well-known substance;
- Σ Like the other penicillins, penethamate is of very low oral toxicity;
- Σ Penethamate is rapidly and completely hydrolysed to benzylpenicillin for which MRLs have been established with benzylpenicillin itself as marker residue;
- Σ Due to the rapid hydrolysis and the low toxicity of penethamate itself the logical marker residue for penethamate is benzylpenicillin.

The Committee for Veterinary Medicinal Products recommends that penethamate is included for bovine species into Annex I of Council Regulation (EEC) No 2377/90 as indicated in the following table :

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Penethamate	Benzylpenicillin	Bovine	50 µg/kg	Kidney Liver Muscle Fat	
			4 µg/kg	Milk	