



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

PROCAINE

SUMMARY REPORT

1. Procaine (p-aminobenzoyl-diethylaminoethanol; synonym: novocaine), is a water-soluble local anaesthetic. Procaine is an amino ester. It is used in cattle, sheep, goats and horses for minor surgical procedures particularly dehorning by subcutaneous injection, and for local and regional anaesthesia by infiltration or nerve block. The common therapeutic doses ranged from 25 to 250 mg per animal. In humans, though procaine formerly was used widely, its use is now confined to infiltration anaesthesia and occasionally for diagnostic nerve block. When it is used as a local anaesthetic, dosages of up to 1000 mg procaine hydrochloride have been used, although doses of 600 mg are more common. In humans, the systemic analgesia can be observed after subcutaneous injection of 100 to 800 mg of procaine.

Procaine is also used as a part of the complex procaine benzylpenicillin, which is an active constituent of various intramammary and parenteral products in veterinary as well as in human medicine. Procaine when combined with benzylpenicillin can prolong the pharmacological effects of benzylpenicillin, reducing the solubility of the latter. This form is an equimolecular mixture of procaine and benzylpenicillin. Procaine benzylpenicillin has the same antimicrobial action as benzylpenicillin, but because of the relatively low blood concentration produced, its use should be restricted to infections caused by micro-organisms that are highly sensitive to penicillin.

2. Procaine acts on the central nervous system, cardiovascular system, neuromuscular junctions and ganglion synapse. Procaine 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. Procaine has a low potency, slow onset and short duration of action. In medicinal products, procaine is used because it possesses vasodilator properties which helps in its rapid absorption after local injection. Procaine has a relatively short action because of hydrolysis by serum cholinesterase but this may be prolonged by up to 45-90 minutes when adrenaline is added. Procaine in the body is mainly hydroxylated in the metabolite para-aminobenzoic acid (PABA) that inhibits the action of sulphonamides; a second metabolite diethylaminoethanol possesses local anaesthetic and antispasmodic activity, but is less effective than procaine in these respects.
3. Pharmacokinetics of procaine, administered either as procaine hydrochloride or as procaine benzylpenicillin, were investigated in laboratory animals (rabbit and guinea pig), horse and humans. Both procaine forms are rapidly absorbed in a variety of animal species following parenteral administration with peak plasma levels being attained within 1 to 3 hours depending on the formulations; effective concentration of benzylpenicillin are usually maintained for 12 to 24 hours.

However, plasma concentrations of benzylpenicillin are lower compared to those following an equivalent dose of benzylpenicillin potassium or sodium. The hydrochloride form could be more rapidly absorbed than the penicillin salt. However, there is only circumstantial evidence that procaine is absorbed following oral administration because it was detected in urine (although not in plasma) of horses and dogs. As procaine is a weakly basic drug with a pK_a of 8.7 (at 20°C) it can be calculated that at the pH's found in the gastrointestinal tract, over 99% would exist in the ionised form and would be absorbed by passive diffusion. Following dissolution of procaine penicillin complex, the procaine is extensively metabolised by enzymes that are present in plasma and in various tissues (including liver) and rapidly eliminated. In humans, the elimination half-life of procaine is less than 1 hour. Procaine benzylpenicillin complex contains between 37.5 and 40.5% w/w procaine.

In the horse, following intramuscular administration of procaine hydrochloride, the half-life was approximately 3 hours and procaine was not detectable by 24 hours post-injection. Procaine is readily absorbed following parenteral administration and thus does not remain long at the site of injection. Its distribution is limited and it is rapidly metabolised. Procaine and its metabolites are predominantly excreted into urine with a rapid excretion. Para-aminobenzoic acid is excreted in the urine to the extent of about 80%, either unchanged or in conjugated form. Only 30% of diethylaminoethanol can be recovered in the urine. The remainder undergoes metabolic degradation. The hydrolysis products of procaine are not toxic. In horses, elimination is generally rapid when procaine is given as hydrochloride but much slower when it is given as the penicillin salt. This same process could be valid for cattle, sheep and pigs. In horses, following intravenous, subcutaneous, intramuscular and intra-articular administration of procaine, the corresponding half-lives were 50.2, 65.7, 125.5 and 97.1 minutes. In the horse, less than 1% of the dose was excreted in urine as parent compound.

In the cat, the liver is responsible for up to 40% of procaine metabolization. In greyhound dogs, hydrolysis of procaine by plasma esterases did not occur; low plasma procaine esterase activity, coupled with rapid oral absorption of procaine, resulted in high urinary concentration of unchanged drug in dogs given procaine hydrochloride. In dogs, following oral administration of procaine hydrochloride (90 mg/kg bw for 3 consecutive days) the urinary concentration of procaine ranged from 0.36 to 68 µg/ml during dosing and from 0.04 to 0.76 µg/ml at 24 hours. Urinary concentrations of procaine were also detectable in greyhound dogs fed with meat prepared from a heifer given procaine benzylpenicillin (44000 IU/kg bw) on 3 consecutive days before slaughter.

No data are available on the metabolism or excretion of procaine following intramammary infusion of procaine benzylpenicillin into either lactating or dry cows. It is known that parenteral administration of penicillin resulted in less than 0.03% of the dose being excreted in milk. It is therefore evident that excretion of penicillin following intramammary infusion is a simple flushing-out of the active substance from teat canal by the milk flow. Once procaine is dissociated from benzylpenicillin, procaine will be soluble at milk pH.

4. Procaine appears as a moderately toxic compound after single administration. The acute intravenous toxicity was low in mice (LD_{50} was 45 mg/kg bw) and in rats (LD_{50} was 35 mg/kg bw). Oral and subcutaneous LD_{50} values in mice were 500 to 1280 and 300 mg/kg bw respectively. The intravenous LD_{50} value for procaine benzylpenicillin was 70 mg/kg bw in mice. In the dog, following procaine intravenous administration at sub-lethal doses of 20 mg/kg bw, tremors of the neck and leg muscles followed by muscle weakness, incoordination and inequilibrium were observed. After intravenous high doses in a range 36 to 80 mg/kg bw dogs became excited and then developed increased extensor tone (beginning in the hind legs), running movements, convulsions and finally respiratory failure. All these symptoms are consistent with the pharmacological action of procaine on the central nervous system. In horses, the administration of procaine hydrochloride intravenously at 2, 5 and 10 mg/kg bw produced behavioural, locomotion and vascular reactions, which were clinically similar to those reported as adverse reactions to procaine benzylpenicillin. The more severe reactions occurred at higher doses, although different horses responded variably at the same dose. Some adverse reactions lead to recumbence but none were fatal.

5. No studies on repeated dose toxicity, reproductive toxicity including embryotoxicity/foetotoxicity and tolerance in target species were presented. Submission of such studies was not considered necessary as procaine has a long history of safe use in human and veterinary medicine and is extensively metabolised and rapidly eliminated. In relation with benzylpenicillin its toxic effects are well-known. The compound itself is of low toxicity.
6. The mutagenicity of procaine was tested in an *in vitro* study. The Ames test (*Salmonella typhimurium* strains TA 100 and TA 98), with and without metabolic activation (rat liver microsomes induced by Araclor 1254 and phenobarbital), did not reveal any mutagenic activity. The maximum non-toxic tested quantity/plate was 20 mg.
7. In view of the rapid elimination of the procaine and the negative findings in the available mutagenicity study, carcinogenicity studies were not considered necessary.
8. No data on the immunotoxicity of procaine were presented. However, it is known that procaine appears to have the ability to produce hypersensitivity reactions in sensitised subjects. Allergic reactions are more common with procaine after parenteral administration. Para-aminobenzoic acid appears to be responsible for these clinical manifestations. Reported data indicate that about 5% of a group of people, who already had been diagnosed as having dermatitis or eczema, reacted positively to a patch test using 2% procaine. At doses between 10 mg and 600 mg rare cases of fatalities have been reported following parenteral administration of procaine.
9. The microbiological properties of procaine are known. *In vitro* procaine hydrochloride, at concentrations of 5% has been shown to be bactericidal and fungicidal, while concentrations of 2% were bacteriostatic. Lower concentrations were without effect. *In vivo* procaine has no effect on the bacteria of human flora.
10. Literature on observations in humans was available. In humans, no adverse effects were observed after a single intravenous administration of procaine at doses of between 2000 and 5000 mg and of procaine benzylpenicillin after a single intramuscular administration of 3 Mega units (equivalent to 1200 mg procaine). In 9 of the 10 patients treated with procaine benzylpenicillin at this regimen procaine was not measurable in the plasma. Rarely, signs of procaine intoxication (which includes convulsions, hypotension and psychosis) may appear. Diethylaminoethanol, a metabolite of procaine, given orally and intravenously to humans at a dose of up to 5600 mg did not produce adverse effects. The common signs seen after administration of high doses of procaine in humans include: nervous, respiratory and cardiovascular alterations and foetal disorders. On the other hand, if procaine is injected intravascularly, ischaemic reactions occur.
11. Residue depletion studies were not available. These studies were not considered necessary since pharmacokinetic data indicate an extensive and rapid metabolism and complete elimination of procaine. With respect to procaine benzylpenicillin, as a worst-case, at any time the molar concentration of procaine in tissues and milk will be equal to that of the benzylpenicillin. Given that the tissues and milk MRLs for benzylpenicillin are 50 µg/kg and 4 µg/kg respectively for all food producing species, the corresponding concentration of procaine (taking into account relative molecular weights) are 40 µg/kg and 3 µg/kg, respectively. In 500 g of tissues (muscle, liver, kidney and fat) and in 1.5 litres of milk, consumers would therefore ingest 25 µg and 4.5 µg of procaine, respectively. This amount is considered of no risk to the consumers. There is also no possibility of an acute risk as the lowest dose recorded as being fatal in humans is 10 mg procaine given parenterally. After an oral dose of procaine, only a small fraction is absorbed. In addition, the withdrawal time fixed for benzylpenicillin will also protect the consumers against potential residues of procaine in food.

Conclusions and recommendation

Having considered the criteria laid down by the Committee for the inclusion of substances in Annex II to Council Regulation (EEC) No 2377/90 and in particular that:

- procaine is extensively metabolised to two metabolites, which are rapidly excreted;
- as local anaesthetic the substance is used in individual animals on an infrequent basis; treated animals are unlikely to be sent for slaughter immediately after treatment;
- procaine benzylpenicillin is a complex, which by hydrolysis is rapidly and completely hydrolysed to procaine and benzylpenicillin; for the latter definitive MRLs have been established with benzylpenicillin itself as the marker residue and benzylpenicillin has already been assessed and is included in Annex I of Council Regulation (EEC) No. 2377/90;
- the small amount of procaine released from the complex procaine benzylpenicillin by hydrolysis has no toxicological risk and procaine residues appear to be unlikely. Likewise, the withdrawal time set for the benzylpenicillin product will protect the consumers against potential residues of procaine in food;

the Committee concludes that there is no need to establish a MRL for procaine when it is used as a local anaesthetic agent and as part of the complex procaine benzylpenicillin and recommends its inclusion in Annex II to Council Regulation (EEC) No 2377/90, in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Procaine	All food producing species	