The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

ATROPINE

SUMMARY REPORT

1. Atropine is an alkaloid extracted from the Belladonna plants that belong to the *Solanaceae* and include *Atropa belladonna* (deadly nightshade), *Datura stramonium* (jimsonweed) and *Hyoscyamus niger* (henbane). Atropine is a racemic mixture of D-hyoscyamine and L-hyoscyamine, racemerization occurring during the extraction procedure. Since atropine is an equal mixture of D- and L-hyoscyamine and the dextro form is biologically inactive, a given quantity of atropine is about one-half as potent as the same quantity of L-hyoscyamine.

   Mostly used in its sulphate salt form, atropine is the prototypical muscarinic blocking agent. The sulphate may contain apotropine, a highly toxic impurity, up to 0.5%.

2. Therapeutically it is used in nearly all food producing animal species either by oral, subcutaneous (even intravenous) or ocular route. Therapeutical indications can be summarised to the following uses: drying secretions, adjunct in gastro-intestinal disorders characterised by smooth muscle spasm, antidote for organophosphorus and other parasympathicomimetic compound poisoning in combination with anticholinesterases, to reverse competitive neuromuscular blockade, as antimuscarinic pre-anaesthetic medication and for pupil dilatation in the case of ocular pathology.

   Doses vary between 0.02 and 0.2 mg/kg bw; by subcutaneous injection: 0.03 to 0.06 mg/kg bw (horse, cattle), 0.03 to 0.16 mg/kg bw (sheep); 0.02 to 0.04 mg/kg bw (pigs). In the case of organophosphorus poisoning the dose can be doubled up to 0.5 mg/kg bw of which one quarter is administered intravenously, the rest subcutaneously. This dose can be repeated 3 to 4 times with an interval of 4 to 6 hours until clinical signs of poisoning are relieved.

3. The interaction of atropine with all muscarinic receptors of smooth muscles, cardiac muscle and glands involves a competitive antagonism with acetylcholine fixation of which, at the level of these receptors is prevented. This leads to an attenuation of the responses to parasympathic nerve impulses.

   Salivary and cholinergic sweat glands are quite susceptible to small doses of atropine, whereas somewhat larger doses are required for a vagolytic effect upon the heart. Gastrointestinal and urinary tract smooth muscles are less sensitive to atropine, and even larger dosages are required to inhibit gastric secretion.

4. A study using radiolabelled atropine in mouse (0.4 to 1.2 mg/animal intravenously and intraperitonealy) showed the highest radioactivity levels in kidney, liver, intestine and lungs and the lowest in the brain. There was also an indication of entero-hepatic circulation resulting in a delay of the removal of atropine and its metabolites from the body. After 3 hours, the total excretion was 60% of the injected activity and 95% after 60 hours.

   In one study 6 ewes had received 0.02 mg/kg atropine sulphate intramuscularly and the following pharmacokinetic parameters have been determined: t_{max} of 13.6 minutes, C_{max} of 7.1 ng/ml, absorption half-life of 2.7 minutes, elimination half-life of 1.6 hours, area under the blood-concentration-time curve (AUC) of 15.3 ng·h/ml, total clearance of 31.2 1/h. In another study, 9 adults sheep, ranging in weight from 50 to 100 kg, had received 2 mg of atropine intramuscularly. The pharmacokinetic parameters were: t_{max} of 2.9 minutes, C_{max} of 11.3 ng/ml, AUC of 1089 ng·min/ml.

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5. In humans atropine is readily absorbed from the gastrointestinal tract. It is also absorbed from mucous membranes, the eye and to some extent through the intact skin. It is rapidly cleared from the blood and is distributed throughout the body. It crosses the blood-brain barrier. It is incompletely metabolised in the liver to tropine and tropic acid. About 60% of the dose is excreted unchanged in the urine. Most of the rest appears in the urine as hydrolysis and conjugation products. A half-life of approximately 2 to 4 hours is reported for men. Atropine crosses the placenta and traces appear in milk.

   Following a single intramuscular dose of 0.02 mg/kg bw the absorption rate and the elimination rate of DL-hyoscyamine (atropine) and L-hyoscyamine (active isomer) were comparable (t_{max} is 8.4 versus 8.7 minutes; elimination half-life 2.95 versus 2.43 hours) but the mean maximum plasma concentration of DL-hyoscyamine (atropine) was 2.9 times and the mean AUC value 6 times higher than that of L-hyoscyamine which indicates a kinetic difference between the enantiomers. The concentrations of D-hyoscyamine reached a maximum between 1 and 2 hours after the drug injection. The renal excretion of L-hyoscyamine occurred mostly in 6 hours (34% of the dose) and no conjugated drug forms were detected.

   Following a single 0.01 mg/kg bw intramuscular dose, a very fast rate of absorption was found with mean peak serum concentrations occurring after only 13 minutes. The elimination half-life was 2.27 hours.

6. Atropine has been used in human medicine orally at doses of 0.2 mg and above, intravenously at doses of 0.4 mg up to 1 mg and subcutaneously at doses of 1 to 2 mg.

   Side effects in humans are mostly in accordance with vagal depression (dryness of the mouth, thirst, mydriasis, bradycardia and constipation.). At therapeutic doses atropine produces minimal effects on the central nervous system. Excessive doses may cause hallucination in humans. Atropine may cause pyrexia as a result of inhibition of sweating even in children receiving topical atropine-containing eye-drops for ophthalmological examination. There is considerable variation in susceptibility to atropine: recovery has occurred even after 1 g, whereas deaths have been reported from doses of 100 mg or less for adults and 10 mg (and even 2 mg) for children. The pharmacodynamic properties presented contained insufficient data to derive a pharmacological NOEL.

7. The LD_{50} for atropine in rats was 3000 mg/kg bw (subcutaneously), 670 mg/kg bw (intragastric) and 620 mg/kg bw (intraduodenally).

8. *Salmonella*-microsomal assay was performed using the strains TA 100, TA 1535, TA 1537 and TA 98 of *Salmonella typhimurium* with or without metabolic activation. Atropine sulphate was found to be non-mutagenic.

   A literature report describes the DNA-cell binding technique for screening potential carcinogens and mutagens using Ehrlich ascites tumour cells and *Escherichia coli* Q13 performed with and without lysozyme and metabolic activation. No DNA-cell binding potential was detected for atropine at concentrations of 10 or 100 μM.

9. There is a considerable interspecies variation in the tolerance for atropine in animals. Herbivorous species are usually much more resistant then carnivores, particularly sheep and rabbits are indifferent to atropine in feed because they synthesise the atropine esterase enzyme. The horse, especially, seems more sensitive to atropine as a dose of more than 0.01 mg/kg subcutaneously can give adverse effects. Indeed, by its paralytic effect on the gastro-intestinal tract, severe colic can be provoked.

10. While studies on repeated oral dose toxicity, reproductive toxicity including embryotoxicity/ foetotoxicity, mutagenicity and carcinogenicity were lacking or insufficient, such studies were not considered necessary for atropine, taking into account the indications for use and the long history of safe use in human and veterinary medicine.

11. While no residue depletion studies were available, those studies were not considered necessary as pharmacokinetic data indicate rapid absorption and elimination of atropine.

Conclusions and recommendation

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

- atropine is rapidly absorbed and eliminated,
- atropine is used for infrequent or non-regular treatments,
- treated animals are unlikely to be sent for slaughter immediately after treatment;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for atropine 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
Atropine	All food producing species	