The European Agency for the Evaluation of Medicinal Products

EMEA/MRL/033/95

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

PAPAVERINE

SUMMARY REPORT

1. Papaverine [$C_{20}H_{21}NO_4$(HCl)] : 1-[(3,4-Dimethoxyphenyl)methyl]6,7-dimethoxy isoquinoline (hydrochloride) is an alkaloid isolated from opium which possesses a smooth muscle relaxant activity with a particularly marked action on blood vessels, especially in the brain.

2. Papaverine is administered by parenteral administration (IM, IV) for the treatment and the prevention of immediate or delayed anoxia in the newborn calf (the only target animal species) at the dose level of 1 to 3 mg/kg b.w.

   Papaverine acts by inhibiting phosphodiesterase responsible for the breakdown of the cyclic AMP. The increase of cyclic AMP concentration in the smooth muscle cells causes a fall in free intercellular calcium and a fall in contractile protein sensitivity ensuring relaxation of the muscle fibres.

3. After an oral administration of Papaverine at the therapeutic dose in man, dog and rat the bioavailability is approximately 60%. The plasma peak is obtained within 1 hour after this administration.

   In dogs, after an intravenous infusion of 35 mg/kg b.w over a period of one hour, Papaverine was found at high levels in liver (75 mg/kg) and fatty tissues (67 mg/kg).

   90 % of the dose absorbed after an oral administration is bioconverted within two hours after the administration by O-demethylation of Papaverine to give phenolic compounds. These compounds are eliminated after glycurono or sulpho-conjugation (inactivation/detoxication).

   The half time elimination is short (2 hours). The elimination is total within 24 hours after the administration.

4. The LD50s were determined in several species and for the different routes. After an intravenous administration, the LD50s in mice, rats and rabbits were 23, 20 and 25 mg/kg b.w respectively. The oral LD50 values were close to 195 mg/kg b.w for mice and 450 mg/kg b.w for rats. The Papaverine acute poisoning causes hypotension, slowed digestive transit, lethargy, dyspnea and death by respiratory failure.

5. In rats, the oral administration of 28 and 167 mg/kg b.w of Papaverine for 3 months did not cause any toxic effects, the weight of the organs and the anatomopathological examinations being normal.

   In the dog, a slight sedative effect was observed without histological or biological disturbances after administrations of Papaverine at 12 mg/kg b.w over a period of 6 months.

6. The Papaverine tolerance in the calf is excellent by the intramuscular route at the therapeutic dose. A single rapid injection IV sometimes may cause transient hesitation or tremors that is not life-threatening for the animal.

7. It was shown that a single subcutaneous injection of 160 mg/kg b.w of Papaverine in gravid mice (9th day of gestation) did not induce malformations of embryos (specially for the central nervous system) collected from uterus of females killed at the 13th day of pregnancy.

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8. The Papaverine gave positive results in the in vitro chromosome aberration test using Chinese hamster fibroblasts cells at 340 µg/ml, concentration largely higher than the cytotoxic one (125 µg/ml). The Ames gene mutation test was negative.

9. Papaverine displays no close structural analogy with any recognised carcinogen and is not reported as being carcinogenic at therapeutic doses.

10. In humans, cases of rare chronic hepatitis are reported after a prolonged administration (more than 1 year) of therapeutic doses (1 to 3 mg/kg b.w, 2 to 3 times a day per os). These phenomenons disappear after the interruption of the treatment.

CONCLUSION AND RECOMMENDATION

Having considered the criteria laid down by the Committee for inclusion of substances into Annex II of the Council Regulation (EEC) N° 2377/90 in particular :

- Papaverine is used in a small number of individual animals. The treatment is given once only (4 injections spread over 48 h) to new born calves.
- The animal is unlikely to be sent for slaughter immediately after treatment.
- This drug is rapidly and extensively detoxified and excreted.

The Committee for Vetertinary Medicinal Products concluded that maximum residue limits for tissues are not necessary to ensure consumer safety and recommends the inclusion of Papaverine in Annex II of Council Regulation (EEC) No 2377/90 as indicated in the following table:.

Pharmacological active substance(s)	Animal species	Other provisions
Papaverine	Bovine	New born calves only