COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

DIPROPHYLLINE

SUMMARY REPORT

1. Diprophylline \((\text{IH}-\text{purine-2,6-dione},7-(2,3\text{-dihydroxypropyl})-3,7\text{-dihydro-1,3-dimethyl})\); (synonyms: glyphylline, glyfyllin and \(7-(2,3\text{-dihydroxypropyl})\text{-theophylline}\)) is a N-substituted theophylline derivative. It is used as a bronchodilator in a variety of diseases, such as asthma, pulmonary oedema and dyspnoea. Diprophylline is administered intravenously in cattle, sheep, horses, goats and pigs as an injectable solution in dosages of 5 to 10 mg/kg bw/day.

In human medicine, the recommended therapeutic oral dose is 200 to 400 mg/person three times a day. (i.e. 600 to 1200 mg/person/day divided in three doses, corresponding to approximately 10 to 20 mg/kg/day).

2. The pharmacological properties of diprophylline were studied in dogs, guinea-pigs, cats, and horses. Diprophylline, a methylxanthine, is a phosphodiesterase inhibitor which prevents the breakdown of cyclic adenosine monophosphate and thus induces relaxation of bronchial smooth muscle. The enantiomers of diprophylline, \(7\text{-}(S)\text{-}(2,3\text{-dihydroxypropyl})\text{-theophylline} (S)\text{-}I\) and \((R)\text{-}I\) showed no differences in the inhibition of 3',5'-cAMP-phosphodiesterase vasodilatatory activity on isolated guinea-pig aorta and on blood circulation in dogs.

The bronchospasmylytic actions of diprophylline administered by intravenous infusion were evaluated in anaesthetised guinea pigs. Diprophylline when given alone at doses of 320 to 640 mg/kg bw had no effect on lung function. High doses caused a fall in blood pressure and an increase in heart rate. However, diprophylline was effective in reducing bronchoconstriction induced by various mediators (histamine, serotonin and bradykinin).

In horses, diprophylline (20 mg/kg intravenously) did not affect heart rate significantly, whereas systolic, diastolic, and mean arterial blood pressures were decreased. The drug did not have significant effect on arterial oxygen tension, carbon dioxide tension, or bicarbonate in these animals.

3. A pharmacokinetic study was performed with rabbits in order to compare the pharmacokinetics of diprophylline and theophylline after intravenous injection. Each rabbit received theophylline (10 mg/kg bw) first and then diprophylline (25 mg/kg bw) two weeks afterwards as an intravenous bolus injection. The serum concentration-time data for both theophylline and diprophylline were best fitted to a two-compartment open model. The elimination half-lives of theophylline and diprophylline were 5.5 and 0.74 hours, respectively. The apparent volume of distribution and total body clearance of diprophylline were 1008 ml/kg and 942 ml/kg/h, respectively, much higher than those of theophylline (545 ml/kg and 69 ml/kg/h, respectively).

In animals, the pharmacokinetics data revealed that diprophylline is not metabolised. The drug is eliminated as the parent compound in the urine. Plasma elimination half-life is very short (about 2 hours) and diprophylline is widely distributed in the body \(V_d = 1.0 \text{ l/kg}\). In horses, the elimination was so rapid that, 8 hours after an intravenous injection of 20 mg/kg (i.e. 2 to 4 times the therapeutic level), plasma concentrations were of about 1 \(\mu\text{g/ml}\).
The pharmacokinetics of diprophylline, including the ratio of diprophylline plasma to saliva levels and the metabolic fate of the drug, were studied in 6 healthy volunteers receiving three 400 mg diprophylline tablets orally with 240 ml of water. Plasma, saliva and urine samples were collected at intervals of time up to 40 hours after dosing and stored until HPLC analysis. Diprophylline absorption was rapid reaching a mean peak plasma level of 21.8 µg/ml at 35.8 minutes. The mean saliva level peak was 11.5 µg/ml which was reached at 43.3 minutes. Mean excreted urinary amount of parent drug for 24 hours was 985 mg (82% of the dose administered). Mean elimination half-lives in plasma and saliva were 2.01 and 2.27 hours, respectively.

Other results in man confirmed these values. In a cross-over study performed in 10 healthy volunteers, the serum and urine samples were analysed after intravenous and oral administration of diprophylline. Disposition of diprophylline showed a two-compartment kinetic profile. After intravenous injection, diprophylline was rapidly distributed and eliminated. The distribution half-life at the a-phase was 0.75 hour and the elimination half-life at the b-phase was 1.7 hours. The mean volume of distribution was 0.70 l/kg and the total body clearance was 0.29 l/kg/h. About 84% of the drug was excreted unchanged in the urine. The drug was almost completely absorbed from the gastro-intestinal tract with an oral bioavailability of about 90%. Mean renal clearance values were higher than paired creatinine clearance values, which is an indication for active renal transport. The rate of protein binding in serum was 75%.

In another human study, 20 normal breast feeding women (age between 20 and 35 years) were treated with a single intramuscular dose of 5 mg diprophylline/kg bw. The distribution of the drug between blood and milk and its elimination were determined. The apparent volume of distribution of diprophylline was found to be 0.505 l/kg, the elimination rate constant was 0.228 h\(^{-1}\), the elimination plasma half-life was 3.21 hours, and the total body clearance was 0.109 l/kg/h. The highest reported blood level for diprophylline is 36.4 µg/ml. The ratio between milk to serum level was 2.08, but the elimination rate from milk was equivalent to that of blood. Thus the maximum milk level for the drug would be in the range of 72 µg/ml.

4. The oral and subcutaneous LD\(_{50}\) values of diprophylline in mice were 3400 and 1430 mg/kg bw, respectively. These data indicated a slight toxicity for diprophylline when administered orally. With dosages in the therapeutic range (20 to 60 mg/kg bw), the rats appeared quite normal in their behaviour. Doses in a range from 100 to 400 mg/kg bw produced little evidence of central nervous system excitation. Observation of the rats up to a period of 30 days after the tests showed no latent toxicity symptoms.

5. No formal repeated dose toxicity studies were presented. Four rats treated with 250 mg/kg bw of diprophylline (12.5 times the therapeutic daily dose) daily over an unspecified period of time showed no death and all rats continued to gain weight. During the toxicity test period the rats displayed little evidence of central nervous system stimulation. Histological examination of the kidneys revealed no tissue damage.

6. A tolerance study was carried out in horses which were treated intravenously with diprophylline at doses of 20 mg/kg bw. Study data indicated that diprophylline could safely be given by rapid intravenous bolus injection to horses in dosages that induce plasma concentrations many times those needed to have the desired effect (10 to 20 µg/ml). Administration was safe even when the drug was injected in less than 15 seconds in dosages of 20 mg/kg bw. From this study, the total dosages administered were 7.7 to 10.9 g and plasma concentrations were as high as 50 µg/kg.

7. No studies on reproductive toxicity, teratogenicity, mutagenicity and carcinogenicity were provided. No information on immunotoxicity and other effects was available. However, in view of the low acute toxicity of the compound, the similarity of the compound to theophylline which has already been assessed and included in Annex II of Council Regulation (EEC) 2377/90 and the use of the compound in human medicine, this information was not considered necessary.

8. No data on the microbiological properties of diprophylline were provided. However, this information was not considered relevant for this compound.
9. No residue depletion studies in target species after recommended dosage were provided. However, due to the rapid elimination of the compound in treated animals, such studies were not considered necessary.

10. No routine analytical method for the detection of residues is available. However, a HPLC analytical method has been used to quantify diprophylline in breast milk of women.

Conclusions and recommendations

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:

- diprophylline is not metabolised and is completely eliminated as such in the urine,
- diprophylline is of low acute toxicity,
- diprophylline is used only occasionally in a small number of individual animals,
- the animals are unlikely to be sent to slaughter during or immediately after treatment;

the Committee considers that there is no need to establish an MRL for diprophylline and recommends its inclusion into Annex II to Council Regulation (EEC) No 2377/90 in accordance with the following table:

<table>
<thead>
<tr>
<th>Pharmacologically active substance(s)</th>
<th>Animal species</th>
<th>Other provisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diprophylline</td>
<td>All food producing species</td>
<td></td>
</tr>
</tbody>
</table>