COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

STRYCHNINE

SUMMARY REPORT

1. Strychnine (CAS No 57-24-9) is a polycyclic alkaloid which occurs in seeds of Strychnos spp., mainly Strychnos nux vomica.

In veterinary medicine strychnine is used in form of the sulphate (approximately 78% alkaloid) or nitrate (approximately 84% alkaloid) salts as a palliative for oral treatment of cattle for stimulation of ruminal motility. It is also used for subcutaneous and intramuscular injection in horses. The claimed indication is symptomatic treatment of locomotor deficits of medullary origin. The daily doses are 5 mg for young cattle and 12.5 mg for adult cattle (approximately 0.025 to 0.1 mg/kg bw). The daily dose for horses is 12.5 mg (approximately 0.025 mg/kg). Maximum intended duration of treatment is 4 consecutive days for ruminants and 5 days in horses.

In human medicine strychnine was used orally as a general tonic and as a bitter to stimulate digestion. The minimum therapeutic dose of strychnine as sulphate for this indication was given with 1 mg/person. The dose range was 1 to 6 mg/person as single daily dose (i.e. 0.017 to 0.1 mg/kg bw) or 3 to 18 mg/person/day when given in fractions. Strychnine has sometimes been used for treatment of non-ketotic hyperglycinaemia of children, an inherited disorder of glycine metabolism, with relatively high oral doses of 0.16 to 2.0 mg/kg/day. Hyperglycinemic children may have an enhanced strychnine tolerance.

2. Strychnine is primarily a competitive antagonist of glycine, the neurotransmitter of inhibitory spinal interneurones and of certain inhibitory neurones in some regions of the brain. Large concentrations of strychnine can apparently inhibit GABA receptors.

Due to the selective blocking of post-synaptic inhibition the level of neuronal excitability in all parts of the central nervous system, especially in the spinal cord, is increased. These central actions of the drug result in a general enhancement of muscle tone. Strychnine does not selectively stimulate the medulla oblongata. However, the medulla is affected at dosages that produce hyperexcitability throughout the central nervous system. Likewise, strychnine does not produce selective gastrointestinal effects. In supraconvulsive doses a curariform action on the neuromuscular junction is observed. Clear dose-effect relationships are not available.

3. Strychnine was reported to be rapidly and almost completely absorbed following oral and parenteral treatment. After oral intake of 700 mg strychnine nitrate by a man in a suicide attempt approximately 90% of the dose was found to be absorbed within 1 hour. Body distribution appears to be rapid: Within 5 minutes after intravenous injection of strychnine to cats (1 mg/kg bw) about 50% of the administered dose had disappeared from blood and after 40 minutes only traces of strychnine were detected in blood samples. In dogs, already 4 minutes after intravenous injection of 50 mg strychnine 7-fold higher concentrations of strychnine are detected in the liver than in blood. In dogs which died of strychnine poisoning, apart from the stomach, highest body concentrations were found in liver followed by kidney and blood.
Metabolism of strychnine was found to be extensive, mainly through oxidation of the molecule by hepatic cytochrome P<sub>450</sub>: In <sup>3</sup>H-strychnine treated rat excreta (0.5 mg/kg bw; subcutaneously) a total of 6 metabolites were structurally identified: strychnine N-oxide, 21α,22α- and 21α,22β-dihydroxy-22-hydrostrychnine and 2-hydroxystrychnine in urine and faeces, strychnine-21,22-epoxide and 16-hydroxystrychnine were only detected in urine. The 21,22- epoxide was the most abundant metabolite. The extractable metabolites in free and/or conjugated form constituted more than 60% of the faecal and urinary radioactivity. About 30 to 40% of the labelled substances in excreta were unidentified water soluble metabolites. Unchanged strychnine was only present in minor amounts with 6% of the dose in urine and 3% in faeces. In vitro studies using liver microsomes provided additional evidence for significant metabolism of strychnine indicating some inter-species differences. Main metabolites were 16-hydroxystrychnine in rats and mice, 2-hydroxystrychnine in guinea pigs and rabbits, and strychnine N-oxide in dogs. The metabolite 18-oxo-strychnine was noted for rabbits only. In addition, several structurally unidentified metabolites were also detected in most species studied.

Excretion of strychnine was found to be rapid and nearly complete: In rats given <sup>3</sup>H-labelled strychnine (0.5 mg/kg bw) nearly all of the dose (approximately 90%) was excreted within the first day post treatment already, approximately 30% thereof in urine and approximately 60% in faeces. Within 7 days excretion of total radioactivity was nearly complete (more than 95%). Unmetabolised strychnine constituted only a minor proportion of the excreted dose (less than 10%). According to observations in humans, relative excretion of unmetabolised strychnine in urine seems to decrease with increasing doses. At an oral dose of 700 mg/person excretion of unchanged drug in 24-hour urine was less than 1%, at oral doses of 4 and 13 to 15 mg/person or intramuscular doses of 4 mg/person excretion of unchanged strychnine in the first 24-hour was 5 to 8%. In a child treated orally with strychnine nitrate for non-ketotic hyperglycaemia for 3½ years, 24 hour urinary excretion of unmetabolised strychnine amounted up to 12% of the administered dose.

4. The acute toxicity of strychnine can vary considerably as concerns the species, strain, sex, age, the individual and route of administration (possibly higher for parenteral administration by a factor up to 10). The following LD<sub>50</sub> values have been reported: mouse: 0.47 mg/kg subcutaneously and 0.75 mg/kg intravenously; rat: 5 to 16.2 mg/kg orally, 1.6 mg/kg intraperitoneally in females and 3.0 mg/kg intraperitoneally in males; dog: 2.0 to 3.9 mg/kg orally. In published literature a single oral dose in the range of 0.5 to 1.0 mg/kg bw is generally held as potentially lethal for mammalian species including humans (approximately 30 to 60 mg/kg person) though considerable higher values have been reported. For instance, in adult humans death has been seen after a dose of 16 mg already while, with appropriate treatment, 2 g strychnine and more have been survived.

In most mammalian species the predominant clinical sign is tonic extension which may develop into symmetrical extensor thrusts and tetanic convulsions. Onset of symptoms usually is within 15 to 30 minutes. Death results from respiratory paralysis and may already occur within 20 to 30 minutes after ingestion of higher doses but may also appear as late as 48 hours after intake of strychnine. The toxicity of metabolites as 2-hydroxystrychnine, 16-hydroxystrychnine and strychnine N-oxide was reported to be much lower than that of the parent compound.

5. An oral repeated dose toxicity study over 28 days was conducted in Sprague-Dawley rats (60 days old). Strychnine hydrogen chloride was administered per gavage at a dose of 2.5 mg/kg bw to females while males received 5 mg/kg bw and 10 mg/kg bw (12 animals/group). Increased muscle tone and slight tremors were observed 10 to 20 minutes after each treatment. These symptoms subsided gradually within the following hour. During treatment 1 rat at 2.5 and 5 mg/kg bw, each, and 5 rats at 10 mg/kg bw died after several doses with signs of acute intoxication. Death was found to occur within 6 hours after dosing. Autopsy of these animals showed pulmonary edema and cyanosis. In the surviving rats no substance-related changes including functional disorders were observed during and at the end of the treatment period (body weight, food/water consumption, behaviour, co-ordination of movement, electrocardiogram, clinical chemistry, pathological/ histopathological examination).
Older studies reported no visible signs of cumulative toxicity following applications of several repeated daily doses (from 2 to 12 daily doses according to individual tolerance) over periods of 1 to 4 days to individual cats (single dose: 0.1 to 0.25 mg/kg bw intramuscularly), dogs (single dose: 0.08 to 0.25 mg/kg subcutaneously), and guinea pigs (single dose: 0.5 to 2.0 mg/kg bw subcutaneously).

No other repeated dose toxicity information was available.

6. From the available data, the potentially lethal oral dose for cattle and horses is reported to be 0.5 mg/kg bw.

7. An ADI based on a complete toxicological profile could not be established from available information. However, overall the available information allows the conclusion that there is no concern for the consumer safety connected to the use of the substance in veterinary medicine.

8. Residue studies for strychnine in edible tissues of target animals were not available but were not considered necessary due to the rapid excretion of the substance. However, considering that after intramuscular and subcutaneous administration, residues might occur at the injection site, the use of the substance should be restricted to oral administration.

9. No analytical method was described but is not considered necessary.

Conclusions and recommendation

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

- strychnine is used only for infrequent treatment of individual animals,
- treated animals are unlikely to be sent for slaughter immediately after treatment,
- the available information indicates that strychnine is rapidly excreted;

the Committee considers that there is no need to establish an MRL for strychnine and recommends its inclusion in Annex II of 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>Strychnine</td>
<td>Bovine</td>
<td>For oral use only at doses up to 0.1 mg/kg bw</td>
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