



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

DETOMIDINE

SUMMARY REPORT

1. Detomidine is used therapeutically for its sedative and analgesic effects in horses and cattle at doses of 10 to 80 µg/kg bw given intravenous or intramuscular injection. Its main therapeutic indications are for analgesia and sedation during diagnostic procedures and minor surgical procedures. It is a potent and specific alpha-2 adrenergic agonist, causing sedation, analgesia, bradycardia, hypotension, diuresis and hyperglycaemia.
2. Several pharmacokinetic studies (rat, dog, calf) were performed with tritium labelled detomidine. Metabolism of the detomidine led to labelling of body water and the studies are therefore difficult to interpret in a quantitative manner. Balance studies failed to account for all the dose administered. With these limitations in mind, it appeared that detomidine was rapidly absorbed (subcutaneous rat, intramuscular cow and horse) and distributed (subcutaneous rat, intravenous dog). Metabolism and excretion were similar in rats and dogs. Detomidine was metabolised by hydroxylation, dehydrogenation and conjugation with glutathione and glucuronide. The majority (60%) of the radiolabelled dose was excreted in the urine during the first 24 h after dosing; between 24 and 48 h a further 2-5% was recovered in urine. Some activity (17.3% rat, 2.6% dog) appeared in faeces suggesting biliary excretion. Further analysis of the residues present in urine is difficult because the extraction method was only 50% efficient for the parent compound and of unknown efficiency for metabolites and about half of the residues in urine were lyophilisable and presumed to be tritiated water. Both metabolites and parent compound were identified in the urine but quantitative estimates are misleading because of the inherent deficiencies in the protocol.

The major metabolites have been shown to be inactive or of much lower pharmacological activity than the parent detomidine.

3. Acute toxicity was related to the pharmacological action. The LD₅₀ in rats (orally, subcutaneous, intravenous), mice (subcutaneous, intravenous) and rabbits (intravenous) ranged from 10-60 mg/kg bw. Pharmacological effects were observed at much lower doses and a pharmacological NOEL was established at 30 µg/kg bw orally in rats (critical parameter - cardiovascular effects). Low oral availability (about 25%) is indicated by the comparison of oral and intravenous doses required for cardiovascular effects in rats and a pilot plasma concentration time-course study in rats. Oral doses have also been shown to be less biologically active than subcutaneous doses in rodents.
4. Repeat dose studies were conducted in the rat (orally -3.5 weeks, subcutaneous 4 weeks) and the pig (intramuscular - 1 month). In all 3 studies, the lowest dose (100 µg/kg bw) produced only pharmacological effects (piloerection and sedation) and the highest dose caused mortality. Repeated dose studies for 90 days in two species were not provided.
5. Two oral teratology studies were performed (rat and rabbit). In the rabbit study, detomidine was non-teratogenic and non-foetotoxic up to 2 mg/kg bw. The NOEL was 0.5 mg/kg bw/day based on maternal toxicity. In the rat study, a NOEL of 0.1 mg/kg bw/day was based on foetal and maternal toxicity and teratogenicity. Both these dose levels are above the NOEL for acute pharmacologic effects.
6. Two-generation-reproduction studies have not been performed. Some reproductive toxicity data in target species (cattle, horses) given detomidine intermittently (at weekly or 4-weekly

intervals) by intravenous or intramuscular routes were provided. These indicated no effect on sperm quality in bulls (37.5 mg/kg bw intramuscular), or on implantation, placental development, early and late pregnancy in cows (50 µg/kg bw intravenous). In the horses receiving 20 µg/kg bw intravenous, 6/10 pregnancies were normal. In the other 4, abnormalities were diverse and their significance is unclear. No fertility disorders, or suspicions of such have been reported as a result of the field use of detomidine. Detomidine is chemically and pharmacologically similar to medetomidine and dexmedetomidine, which have been shown to have no effect on male and female fertility in rats.

7. Detomidine was not mutagenic in the Ames test in the presence and absence of metabolic activity (S9). Very high concentrations (0.3 mg/ml) produced chromosomal aberrations in an *in vitro* CHO assay in the absence S9, but this effect may be attributed to non-specific pH effects. Lower concentrations (0.2 mg/ml) or the addition of S9 with the high concentration were not clastogenic. Detomidine at up to 20 mg/kg was not mutagenic in an *in vivo* mouse micronucleus test; bone marrow toxicity was not demonstrated but it is unlikely that detomidine was unable to reach these cells.
8. No carcinogenicity studies were performed.
9. Although no formal study was presented, there were no indications that detomidine causes immunotoxicity.
10. Detomidine was not tested for anti-microbial activity but alpha-adrenergic agonists are not known to possess such activity.
11. The structurally related compounds medetomidine and dexmedetomidine have been used in humans. These drugs are 1-10 times more potent than detomidine in a range of experimental animal models. In humans, both caused bradycardia and hypotension at 0.167-0.21 µg/kg bw intravenous. Medetomidine at 0.67 µg/kg bw intravenous caused hypotension and sedation that lasted for at least 8 h. Dexmedetomidine at plasma concentration of 10 µg/ml lowers plasma noradrenaline concentrations; at concentrations of 50-100 µg/ml, other pharmacological effects are seen. A NOEL for intravenous medetomidine of 125 ng/kg bw has been established in humans. Taking a conservative value for the relative potency of detomidine to medetomidine of 1.0 and a conservative value of 1/3 for the bioavailability of oral relative to intravenous doses, the ADI for oral detomidine may be calculated as :

$$\begin{aligned}
 \text{NOEL of intravenous medetomidine in humans} &= 125 \text{ ng/kg bw} \\
 \text{proposed ADI for oral detomidine} &= 125 \times 1 \times 3 \text{ ng/kg bw} \\
 &= 0.375 \text{ µg/kg bw} \\
 &= 22.5 \text{ µg/person}
 \end{aligned}$$

12. The ADI can also be calculated from acute cardiovascular effects of detomidine in rats following oral dosing (NOEL is 30 µg/kg bw). Safety factors of 10 for species differences and 10 for individual variation should be applied. This gives a value for the NOEL for a 60 kg bw person as follows :

$$\frac{30 \times 60}{10 \times 10} = 18 \text{ µg/person}$$

13. Residue studies were conducted in cattle and horses using either tritiated detomidine (where labelling of body water was evident) or radioimmunoassay (where the specificity of antiserum is such that the major metabolites are not detected). Elimination is biphasic, the initial rapid phase ($t_{1/2}$ 2 h; CL 10 ml/kg/min, V_d 3 l/kg) comprising redistribution from the plasma and elimination and a slow phase ($t_{1/2}$ 20 h, CL 25 ml/kg/min, V_d 29 l/kg) which predominates 6-8 after a 50 µg/kg dose, when the plasma concentration has fallen to 0.2 ng/ml. These values may be subject to error because of the labelling of body water.

14. Metabolites were identified in the urine of horses but none were found in the tissues of cattle or horses. The residues found could be entirely accounted for by detomidine itself and tritiated water. The highest levels were found in the liver, followed by kidney, muscle and fat. There was no excess of residues at the injection site. The measured residues of detomidine may be underestimated because of loss of label to tritiated water. Using the RIA method, residues found in cattle and horses and after intramuscular and intravenous injection were all similar. The highest reported value was 5.9 µg/kg in horse liver 24 h after intramuscular dosing. At 48 hours, the levels were mostly at or below the detection limit (0.35 µg/kg). Residues in milk were 0.6 µg/kg 7 h after intramuscular injection and undetectable at 23 h after treatment.
15. The values from the RIA for the potential residues in cattle and horses and from the radiotracer study in cattle, assuming the total non-volatile radioactivity measured in tissues is parent detomidine, can be used to obtain a worst estimate of the intake of detomidine 24 h after dosing.

Species	Source of data	detomidine in daily meat package (µg/person)
horse	RIA	1.04
cattle	RIA	0.429
cattle	total non-volatile residues in radiotracer study	1.71

16. It is recommended that tissue maximum residue limits are not required to ensure consumer safety and that therefore detomidine be entered into Annex II of Regulation 2377/90 EEC for use in cattle and equidae. The reasons are summarised below :
- the major effects are pharmacological not toxicological
 - the drug is intended for single use on individual animals
 - the drug does not remain concentrated at the injection site
 - the drug and its metabolites are rapidly excreted such that residues present in tissues by 24 h after dosing are below the proposed acceptable intake.

Member States may wish to consider setting withdrawal periods at the stage of marketing authorisation.