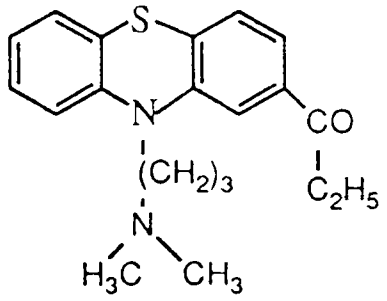
PROPIONYLPROMAZINE

IDENTITY

Chemical: 1[10[3-(dimethylamino)-propyl]-1OH-phenothiazin-2-yl]-1-propanone.

Synonyms: Propiopromazine

Structural formula:



Molecular formula: $C_{20}H_{24}N_2OS$

Molecular Weight: 340.6

OTHER INFORMATION ON IDENTITY AND PROPERTIES

Pure Active Ingredient:

In veterinary preparations the phosphate or hydrochloride salt is used and formulated as a 1% aqueous injectable solution.

Appearance: Propionylpromazine is slightly yellow crystalline powder.

Melting Point: 69-70^{o}

RESIDUES IN FOOD AND THEIR EVALUATION

CONDITIONS OF USE

Propionylpromazine is used as a neuroleptic to combat stress in pets and farm animals. The main use is to combat stress in the transport of pigs especially during transport to the slaughterhouse, thereby reducing the incidence of death or a deterioration in the quality of the meat.

Dosage

Propionylpromazine may be administered as an injection of a 1% aqueous solution of the salt either intravenously (IV), subcutaneously (SC) or intramusculary (IM).

The dose varies with the route of administration and the species.

	Dose (mg Propionylpromazine per kg)		
Species	**IV**	**IM**	**SC**
Horse	0.05 - 0.1	0.05 - 0.1	-
Cattle	0.1 - 0.2	0.1 - 0.2	0.2 - 0.5
Pig	0.2 - 0.3	0.3 - 0.5	0.5 - 2

METABOLISM

Pharmacokinetics

50 mg Propionylpromazine was injected IM to a horse and the concentration of Propionylpromazine measured in plasma samples collected at intervals for an 11 hour period (Park et al., 1989). The concentrations were measured by gas chromatography using a nitrogen-phosphorous detector. The LLD was 0.2 μg/L.

The peak concentration (5.2 μg/L) was seen at 30 minutes WT decreasing to 1.26 μg/L at 11 hours WT. No other pharmacokinetic parameters were determined.

Metabolism in Animals

Information on the metabolism of Propionylpromazine in animals is limited to one study in a horse (Park et al., 1989) and the possibility that the sulphoxide may be a metabolite in the pig (Arneth, 1986). 50 mg Propionylpromazine was injected IM to one horse and the urine examined for parent drug and metabolites. The time of the urine collection is not stated. After enzyme hydrolysis the parent drug urine and three metabolites were identified by gas chromatography - mass spectrometry (GCMS). The metabolites were 2-(1-hydroxypropyl)promazine, 2-(1-propenyl)promazine and 7-hydroxy-Propionylpromazine.

No N-demethylated or sulphoxidated metabolites of Propionylpromazine were observed in the horse but Arneth (1986) found very small amounts of the sulphoxide especially in spare rib tissue. Exposure of Propionylpromazine to light and air also results in the formation of minute quantities of the sulphoxide (Haagsma et al, 1988) and thus the presence of this metabolite may be due to an artifact.

TISSUE RESIDUE DEPLETION STUDIES

There are no radiolabeled residue depletion studies available.

Other Residue Depletion Studies with unlabeled Propionylpromazine.

There was no specific study to measure the distribution of residues in animals, the two sets of results given below are data derived in the testing of chromatographic methods for measuring Propionylpromazine.

Six female and six castrate male Dutch Landrace pigs weighing 100 kg were injected deep into the muscle behind an ear with 0.5 mg Propionylpromazine per kg BW. The animals were slaughtered in groups of four (2M and 2F) at 2, 8 and 24 hours after injection. The concentrations of Propionylpromazine was measured by densiometric TLC in four tissues and the results are detailed in table I. (Olling, Stephany and Rauws, 1981). There is a tendency for the concentrations in kidney and liver samples of the female pigs to be higher than those in the male samples.

Table I. Propionylpromazine concentrations (μg/kg) in pig tissues.

WT (hours)	Sex	Kidney	Liver	Brain	Diaphragm	Injection Site (mg total)
2	F	340	260	210	50	28.7
2	F	340	300	200	30	10.2
2	M	90	80	210	70	24.0
2	M	90	70	130	50	23.6
8	F	150	200	190	50	15.0
8	F	150	240	130	30	21.4
8	M	50	80	190	60	18.5
8	M	110	170	180	60	22.1
24	F	50	240	40	<10	4.6
24	F	40	370	50	10	7.4
24	M	40	120	50	10	8.3
24	M	80	190	100	20	2.6

Also in the same paper female Wistar rats were administered Propionylpromazine in the tail vein at a dose of 4 mg/kg BW. The mean values ± SD for the residues in the rats are shown in Table II.

Table II. Propionylpromazine (mg/kg) in rat tissues after IV injection of 4 mg/kg BW

WT (hours)	n	Kidney	Liver	Brain
0.2	4	16.2 ± 4.8	1.3 ± 0.4	5.6 ± 1.3
0.5	4	9.9 ± 3.2	1.2 ± 0.2	5.4 ± 0.8
1.0	4	7.0 ± 3.0	1.1 ± 0.3	2.7 ± 0.4
2.0	4	3.3 ± 1.5	0.6 ± 0.2	0.6 ± 0.2

A second study investigated the residues of several tranqilizers in pigs 8 hours after IM injection. Propionylpromazine was administered to three pigs at a dose of 0.5 mg/kg BW. The presence but not the quantity of residues of Propionylpromazine were determined by a TLC method with a LLD of 60 g/kg. The pigs were slaughtered at 2, 5 and 8 hours after injection and Propionylpromazine was found to be present at the injection site and in the kidneys in each of three pigs. Propionylpromazine was present

in the diaphragm muscle in the pigs at 2 and 5 hours WT but not in the muscle of the pig killed at 8 hours WT (Haagsma, Bathelt and Engelsma, 1988).

METHODS OF ANALYSIS FOR RESIDUES IN TISSUES

Three types of chromatographic methods are used by at least six EEC Member States to screen for residues of Propionylpromazine in food-producing animals. The most widely used technique is HPLC for residues in muscle or kidney tissues, one country uses TLC and another GLC. The LLD of the methods is 4 g/kg for TLC, 0.1 - 50 g/kg for HPLC and 10 - 50 g/kg for the GLC method. Between 5 and 20 g of sample is needed for an analysis. (EEC Handbook, Residues in Food Producing animals and their products: Reference materials and methods, Ed. R.J.Heitzman, to be published).

A TLC procedure was described (Haagsma et al, 1988) for the detection of Propionylpromazine and other tranqilizers and carazolol in pig muscle and kidney with a detection level of 25 g/kg. 20 g of tissue are ground up with alkali and extracted with ether. After washing with petroleum ether the extract is run through a silica gel solid phase extraction (SPE) column and the Propionylpromazine eluted with methanol. The volume was reduced and any precipitate removed before applying the majority of the extract to an HPTLC plate. The plate was developed in two dimensions using 1) CH_2Cl_2:acetone:25% ammonia::100/100/5 v/v and 2) n-butanol:acetic acid:water::80:20:100 v/v. The spots were viewed under UV light.

An older TLC method was reported by Olling et al., (1981) for the specific determination of Propionylpromazine in pig tissues. 5 to 10 g of liver, kidney, muscle or brain tissue was ground with sand and extracted with solvent/solvent partition systems. An aliquot was run on a monodimensional polyamide TLC plate using cyclohexane:$CHCl_3$:ammonia (14 mol per L)::90:20:20:0.25 v/v/v/v. The LLD was 2 - 20 g/kg.

An HPLC method was reported for measuring Propionylpromazine and other tranqilizers and carazolol in pig kidneys with a level of detection of 4 g Propionylpromazine per kg (Keukens and Aerts, 1989). The procedure involves extracting 5 g kidney with acetonitrile, rapid sample clean-up with a SepPak C18 cartridge and HPLC with UV or fluorescent detection. The mean recoveries of Propionylpromazine using a 20 g/kg spike were 95% with a CV = 6.7% for 10 tests. The method was tested in a routine monitoring programme on more than 1000 samples and 30 samples per day could be analysed. The method was claimed to be successfully applied to injection sites, plasma and liver samples. The possible use of a diode array detector will improve the specificity of the method.

A GLC method was used to measure Propionylpromazine concentrations in plasma of a horse with a lower limit of detection of 0.2 g/L. (Park et al., 1989). Hartvig et al., (1980) also describe a GLC method for plasma with an LLD of 10 - 20 g/L but unfortunately nowhere in the publication is the species used mentioned.

APPRAISAL

There is insufficient information available on the pharmacokinetics, metabolism and depletion of the residues to establish a meaningful MRL. There are good monitoring

methods for detecting the presence of residues of Propionylpromazine in treated pigs and it should be possible to control some conditions of use, e.g. over short withdrawal times in pigs.

REFERENCES

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