ISOMETAMIDIUM CHLORIDE

IDENTITY

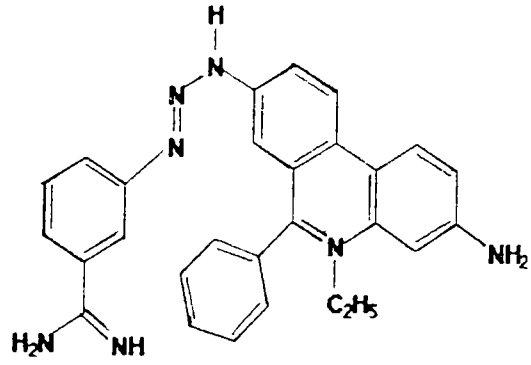
Chemical name: 3-Amino-8-[3-[3-(aminoimiinomethyl)phenyl]-1-triazenyl]-5-ethyl-6-phenylphenanthridinium chloride

8-[3-(m-amidinophenyl)-2-triazeno]-3-amino-5-ethyl-6-phenylphenanthridinium chloride

7-m-amidinophenyldiazoamino-2-amino-10-ethyl-9-phenylphenanthridinium chloride

Synonyms: Samorin and Trypamidium

Structural formula:



Molecular formula: $C_{28}H_{26}ClN_7$

Molecular weight: 496.04

OTHER INFORMATION ON IDENTITY AND PROPERTIES

Pure active ingredient

Appearance	Red crystals from aqueous methanol
Melting Point	Decomposes 244-245°C

Technical Active Ingredients

The commercially available products Samorin and Trypamidium have isometamidium chloride as the principle component with the remaining fraction comprising of two isomers, two analogs of a bis-species, and homidium. Isometamidium is presented as a dark reddish-brown powder with a solubility in water of 6% (w/v) at 20°C.

RESIDUES IN ANIMALS AND THEIR EVALUATION

CONDITIONS OF USE

General

Isometamidium is an antitrypansmal agent. It is used for the treatment and prevention of animal trypanosomiasis principally in cattle but also in sheep, goats, buffalo, donkeys, horses, camels and dogs. Activity has been demonstrated against Trypanosoma congolense, T.vivax, T.brucei, and T.evansi (Touratier, 1981).

Dosages

Isometamidium is prepared as a 1%, 2% or 4% (w/v) injectable aqueous suspension to be administered intramuscularly at a dose rate of 0.5 or 1.0 mg/kg body weight. Occasionally it is administered by intravenous injection (Dowler, et al., in press). For intravenous use in cattle, isometamidium is used as a 1% aqueous solution to be administered at 0.6 mg/kg.

Pharmacokinetics and Bioavailability

The distribution and elimination of isometamidium was examined in lactating dairy cattle following intramuscular injection, 1.0 mg/kg, of 14C labeled material (Bridge, et al, 1982). Peak concentrations of radio-labeled products were detected in plasma at 24 hrs (0.027 mg/ml) post dose and steadily declined to the limit of detection (0.01 mg/ml) by 29 days.

Kinabo and Bogan (1988b) investigated the absorption and distribution of isometamidium and its effect on tissues in cattle following intramuscluar injection at 0.5 mg/kg body weight. The drug was rapidly detectable in serum at a mean concentration of only 20 ng/ml and declined to concentrations of lower than 10 ng/ml within two hours. After 120 hours, serum levels of isometamidium were below the limit of detection.

The absorption of 14C-isometamidium was investigated in female rats following a single 1 mg/kg oral dose (Smith et al., 1981). Minimal absorption of the dose was observed. By day 7 after dosing, all tissues contained less than 10 ng/g, at which time 99% of the administered dose had been voided in the feces.

METHODS OF RESIDUE ANALYSIS

Earlier analytical procedures lacked sensitivity and specificity such as the spectrophotometric method described by Philips et al,, (1967) which could not detect isometamidium concentrations less that 1 mg/ml in the plasma. The HPLC method developed by Perschke and Vollner (1985) was indirect in that isometamidium was converted to homidium before assay and therefore not specific.

Most of the methods reported for isometamidium, or isometamidium isomers and analogues, are for levels in plasma or serum. Kinabo and Bogan (1988a) have developed an analytical procedure using solid-phase extraction and ion-pair reverse phase HPLC with fluorescence detection for isometamidium in bovine serum and tissues. Although the assay could detect levels of isometamidium down to 10 ng/ml in serum, the sensitivity was limited to 500 ng/g in the tissue. The authors suggest that this may be due to strong binding of isometamidium to mucopolysaccarides, nucleic acid and lipids.

METABOLISM AND RESIDUE STUDIES

Metabolism Studies

The metabolism of isometamidium has not been extensively studied. However, studies with rats (Philips, et al.,1967) and cattle (Kinabo and Bogan, 1988b) have indicated that isometamidium metabolites could not be found in the blood. The latter study indicated the injection site was the primary depot for prophylaxis. The presence of active metabolites would have been suspected if isometamidium concentrations at the injection site were as transient and low as those in serum.

Residue Studies

In the pharmacokinetic study described previously, Bridge et al. (1982) found the highest concentration of radioactivity, 73.5 mg/g, was located at the injection site 72 hours post-injection. The half-life of the injection site residues were calculated to be 39 days. The liver and kidney tissues were the other main sites of radioactivity localization. The peak concentrations of isometamidium equivalents were 7.1 and 5.8 mg/g at 72 hours with elimination half-lives of 25 and 35 days for the liver and kidney tissues

respectively. In addition to tissues, milk samples were collected and analyzed during the 90 day post injection period. Most of the samples had levels of Isometamidium which were below the limit of detection (0.01 mg/ml). However, some cows did produce positive samples (0.0138 - 0.0174 mg/ml) on single occasions from 5 to 70 days post-injection.

Isometamidium residues in calves have been reported using a sensitive HPLC method (Kinabo and Bogan, 1988b). In this study the calves were administered isometamidium at 0.5 mg/kg by intramuscular injection. Isometamidium was only detectable in the serum up to 2 hours after injection, at a mean maximum concentration of 20 ng/ml. The highest concentration of Isometamidium was detected at the injection site at 7, 21 and 42 days. The results of the various tissue assays have been tabulated in Table I.

Table I. Isometamidium residues in calves (µg/g)

Tissue	Days Post-injection 7	21	42
Injection site	1270 ± 272	315 ± 173	208 ± 94
Liver	4.80 ± 0.84	4.07 ± 0.35	.75 ± 1.41
Kidney	5.21 ± 3.36	2.98 ± 0.64	0.70 ± 0.11
Spleen	3.10 ± 1.52	2.75 ± 2.47	0.82 ± 0.07
Muscle	1.00 ± 0.02	0.87 ± 0.01	0.59 ± 0.12
Heart	0.40 ± 0.04	0.31 ± 0.08	0.20 ± 0.23

Isometamidium residues in goats treated by intramuscular and intravenous injection at a level of 0.5 mg/kg were evaluated using a spectrophotometric method (Braide and Eghianruwa, 1980). Table II shows the concentrations of isometamidium found in tissues 4 and 12 weeks after a single dose.

Table II. Isometamidium residues in goats (mg/g)

Tissue	Time (weeks)	Route of Administration: Intramuscular	Intravenous
Liver	4	5.52 ± 0.38	11.39 ± 0.61
	12	ND	6.78 ± 0.29
Kidney	4	2.51 ± 0.16	9.29 ± 0.52
	12	<1.25	3.26 ± 0.20
Spleen	4	<1.25	ND
	12	—	—
Muscle	4	ND	ND
	12	—	—
Fat	4	ND	ND
	12	—	—
Injection Site	4	2.51 ± 0.21	ND
	12	ND	—

(Note: ND = Not detected)

APPRAISAL

There are numerous deficiencies with the residue data for isometamidium; however, the resolution of these deficiencies would not decrease the residue levels experimentally determined in edible tissues. Firstly, the specifications for the commercial product indicate a minimum purity of only 70%. While colorimetric, chromatographic and

radiometric methods may detect isometamidium and the other components of the product in the tissues, the residue depletion levels varied dramatically even within a single species. Secondly, there is a lack of metabolism data to characterize what metabolites contribute significantly to the residue levels. Thirdly, the predominate conditions of use of the drug are unclear. Although it has been stated that intramuscular injection is the routine route of administration, it has been noted that intravenous injection has been used on a therapeutic basis since 1985.

The intramuscular use of isometamidium in food-producing animals results in significant and persistent residues at the injection site, liver and kidney tissues. Intravenous injection produces even higher and more persistent residues in the liver and kidney. Manufacturers of isometamidium recommend that animals not be slaughtered for human consumption within one month of treatment. Depending on the toxicological evaluation, the injection site, liver and kidneys of treated animals should be discarded prior to human consumption.

REFERENCES

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