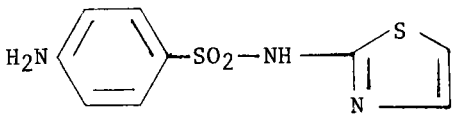
SULFATHIAZOLE

IDENTITY

Chemical name: 4-amino-N-2-thiazolylbenzenesulfonamide

Structural formula:



Molecular formula: $C_9H_9N_3O_2S_2$

Molecular weight: 255.32

OTHER INFORMATION ON IDENTITY AND PROPERTIES

Pure active ingredient

Melting point 200-204°C

RESIDUES IN ANIMALS AND THEIR EVALUATION

PHARMACOKINETICS

Pigs

The pharmacokinetics of sulfathiazole (STZ) in swine following both parental and oral administration of the drug have been well investigated. The data obtained fit simple pharmacokinetics models. These models permit prediction of residue depletion.

Pigs - Parental Administration

Pigs (33-40kg) were injected into the femoral vein with a single dose of a 12.5% solution of sodium salt of STZ equivalent to 72mg per kg live weight. Blood and urine samples were collected for 25 hours and analysed for residues of STZ. The biological half-life was 1.4 hours and the volume of distribution was 0.54 L/kg. Within 12 hours of administration the STZ in plasma was no longer detectable and the excretion of residues into the urine was complete.

The amount of residues in the urine as a percentage of the original dose were:

STZ 60%; Acetyl-STZ 23%; Polar metabolites 3%

Thus about 86% of the dose was excreted into the urine within 12 hours and the remainder was excreted by an extrarenal route (Koritz et al, 1978).

In a further study by the same group, pigs (32-36 kg) were administered the same dose as above and slaughtered 2-24 hours after dosing. The half-life of STZ was 1.6 hours and the volume of distribution 0.625 L/kg.

The cumulative excretion of residues into urine again reached plateau values about 12 hours after dosing with STZ = 48% dose; and the acetyl-STZ = 19% original dose.

Concentrations of STZ were measured in muscle, liver, kidney and fat and the data for all tissues was closely correlated ($r > 0.994$ see table I) with the plasma concentration and the rate of excretion into the urine. This indicates that STZ rapidly penetrates and

equilibrates with a large number of extravascular tissues. The authors concluded that using simple pharmacokinetic models the tissue residues can be estimated with accuracy from plasma and/or urine concentrations of the drug and a valid estimate can be made of the time required for tissue residue depletion to tolerance without slaughtering the animals (Bourne et al, 1978).

Table I: STZ concentrations in tissues and fluids of pigs after intravenous administration of 72 mg STZ-Na per kg live weight

Hours after dosing	Muscle (ppm)	Liver (ppm)	Kidney (ppm)	Fat (ppm)	Plasma (ppm)	Excretion rate (% dose/hr)
2	24.8 (2.8)	37.5 (2.2)	147 (51.3)	9.1 (1.6)	44.9	9.37
4	7.9 (1.6)	15.6 (2.9)	46.5 (7.7)	6.2 (1.9)	18.9	4.58
8	1.2 (0.2)	2.9 (0.3)	7.7 (0.8)	0.5 (0.1)	4.4	1.14
16	0.2 (0.15)	0.3 (0.12)	1.3 (0.3)	n.s.	0.8	0.11
24	0.15 (0.1)	n.s.	n.s.	n.s.		
r between plasma and tissues	0.996	1.000	0.994	0.940		
r between excretion rate and tissues	0.986	0.997	0.985	0.961		

Each value is the mean of three animals with the standard deviation in parentheses.
n.s. indicates the means are not significantly different ($p < 0.01$) from the mean value for three control untreated pigs.

r is the correlation coefficient.

Residues measured by method of Annino, (1961).

Pigs - Oral Administration

Pigs (33-40 kg) were given a single capsule by gastric intubation of a solution of sodium salt of STZ equivalent to 214 mg per kg live weight. Plasma concentrations of STZ and urinary concentrations of residues were measured over a 24 hour period after dosing. The half-life of absorption was 0.8 hours and about 73% of the original dose was excreted in the urine within 24 hours. There was almost 3 times as much parent STZ as the acetyl-STZ in the urine with only a few percent of the residues excreted as polar metabolites.

Thus the sodium salt of STZ is rapidly absorbed from the gut and is rapidly excreted undergoing some metabolism into the urine. (Koritz et al, 1978).

In an earlier study 16 pigs (43-53 kg) were given sodium-STZ in capsule form at a therapeutic level (330 mg per kg live weight) for 3 days. A 12 hour dosing schedule was used. The pigs were slaughtered at regular intervals over a 12 day withdrawal period. Tissue and urine samples were collected and analysed for residues of STZ. The results are shown in Table II.

The concentrations of STZ were very high in all tissues and urine of the pigs slaughtered within 12 hours of drug withdrawal. Thereafter there was a rapid decline in the residues

such that although residues were detected at day 7 no residues in the tissues were found at the next sampling points, days 10 and 12 (Righter et al, 1971).

Table II. Residues of sulfathiazole in pig tissues and urine after three daily oral doses of sodium-STZ at 330 mg per kg live weight

Withdrawal period (days)	N	Residues (ppm) Muscle	Liver	Kidney	Fat	Urine
0.5	2	2.8 (5.6)	17 (20)	60 (74)	3.0 (3.7)	1405*
3	2	0.06 (0.12)	0.06 (0.11)	0.04 (0.05)	0.1 (0.17)	87.3*
5	3	0.03 (0.07)	0.01 (0.04)	0.06*	0.06 (0.07)	33.2*
7	3	0.11 (0.12)	0.02 (0.04)	0.04 (0.04)	0.13 (0.14)	-
10	3	0.00 (0.01)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	6.0 (12.2)
12	3	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.000)	-

All values are means except those marked* which are results for only one pig.
N is number of pigs.
The values in parentheses are the maximum values.
Residues determined by method of Annino, (1961).

Ruminants

The pharmacokinetics of STZ were studied in four sheep (ewe-lambs 27-32 kg). STZ was administered as a 5% solution of the sodium salt into the jugular vein and orally as a 12.5% aqueous solution of the sodium salt. The doses were either 36 or 72 mg per kg for the i.v. injections or 214 mg per kg oral intubation.

Blood and urine were collected over 48 hour period for the i.v. dose and 144 hour period for oral dose.

Plasma and urine data were examined. The pharmacokinetics can be described by a one compartmental model. The semi-log plot of the average concentrations of STZ in plasma and also the amount of unchanged STZ excreted into the urine were linear with time in both the i.v. treatments and after 4-6 hours in the oral treatments.

STZ was rapidly eliminated with a biological half-life of 1.3 hours. After oral administration it was absorbed slowly (half-life 18 hours) and 73% was excreted in the urine. Following oral administration the disappearance of STZ from the plasma was controlled by the rate of drug absorption, rather than by elimination.

The major components in the urine were unchanged STZ and the acetyl derivative. STZ was 5-9 times more abundant than Acetyl-STZ. Polar metabolites were also measured and usually made up <5% total residues (Koritz et al, 1977).

The plasma, tissue and urine STZ concentrations were determined at various times following intravenous administration of STZ-Na (72 mg per kg) to 12 female sheep.

The plasma and urine data were consistent with a one-compartment pharmacokinetic model, with an elimination half life of 1.1 hour. After 10 hours 87% of the original dose, wax excreted into the urine. 67% original dose was STZ, 18% was the acetyl-STZ and about 2% was an unidentified polar metabolite.

The data from the tissue sites (see table III) also were consistent with the one-compartment model and confirmed that tissue residues of STZ can be calculated from urine and plasma concentrations. The correlation coefficients (see table III) for the concentrations between the fluids and the tissues all exceeded 0.994 (Bevill et al., 1977 b).

Table III. STZ concentrations in tissues and fluids of sheep after intravenous administration of 72 mg STZ-Na per kg live weight

Hours after dosing	Muscle (ppm)	Liver (ppm)	Kidney (ppm)	Fat (ppm)	Plasma (ppm)	Excretion rate (% dose/hr)
2	22 (5.7)	40 (13)	308 (145)	11 (5.2)	47	13.4
4	4.9 (2.8)	9.4 (4.9)	55 (24)	3.5 1.9)	12	4.3
8	0.23 (0.11)	0.70 (0.29)	2.3 (1.3)	0.26 (0.13)	1	0.7
16	0.05 (0.02)	0.30 (0.14)	0.36 (0.13)	n.s.		
24	n.s.	0.12	0.11	n.s.		
r between plasma and tissues	0.999	1.000	1.000		0.998	
r between excretion rate and tissues	0.995	0.996	0.990		1.000	

Each value is the mean of three animals with the standard deviation in parentheses.
n.s. indicates that the means are not significantly different ($p < 0.01$) from the mean value for three control untreated sheep.
r is the correlation coefficient.
Residues measured by method of Bevill et al (1977a).

Humans

The kinetics of excretion into urine and acetylation were studied in normal adult humans. Excretion of free STZ, it's acetylation, and excretion of acetyl-STZ were described by a kinetic model previously shown to hold for the same processes in the disposition of sulfisoxazole and sulfamethylthiadazole when 0.5 gram doses were ingested. The disposition of these drugs by the human consists of two competitive first-order processes, one for acetylation and the other for excretion of the free drug.

Normal adults were given oral doses (0.5 - 1 g) of STZ and the amounts of STZ and acetyl-STZ measured in regular urine samples collected over a 36 hour period. The cumulative amounts of drug after 36 hours are shown below:

Dose (mg)	STZ (mg)	Acet-STZ (mg)	Total mg	% Dose
1000	800	232	1032	103
1000	786	213	999	100
500	408	67	475	95
500	451	79	530	106
500	452	79	531	106
500	371	141	512	102

Acetyl-STZ is calculated as the free drug.

The experimental data fitted the theoretical predictions escept in the first subject receiving a one gram dose. This was because the intake of water was insufficient to maintain a urine flow rate high enough to prevent crystalluria. When the experiment was repeated at a higher water intake the model was obeyed. At a 1 gram dose it was calculated that urine excretion rate must exceed 200 ml per hour to maintain solubility of the acetyl-STZ (Nelson, 1961).

RESIDUES

Metabolism of STZ

There are numerous reports that the major metabolite of STZ in man, rats, pigs, sheep, cattle and rabbits is the N-acetyl derivative.

There is evidence of a small percentage of polar metabolites formed in the pig, sheep and human. Willians (1959) suggests that the polar metabolite in humans is produced by the hydroxylations of the 2-position on the aromatic ring.

Appraisal

The results of two studies in pigs and one in sheep are shown in tables I, II and III. Unfortunately there does not seem to be a definitive radiometric study and only one study where STZ is administered orally in pig feed.

Residues in tissues of pigs (see table II) fed 330 mg STZ per kg live weight were highest in liver (maximum 20 ppm) and kidney (maximum 74 ppm) 12 hours after withdrawal of the drug. The concentrations declined very quickly and in all tissues were <0.18 ppm 3 days after withdrawal and only detectable in one muscle sample (0.01 ppm) after 10 days withdrawal time.

The residues following large intravenous injections of STZ into both pigs (table I) and sheep (table III) produced very high residues for the first few hours after administration but then the drug was rapidly excreted and the residues were ca. 0-0.3 ppm 24 hours after dosing.

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