PA 19140.
Accepted for publication June 22, 1976.
Presented at the Pharmacology and Biochemistry Section, APhA Academy of Pharmaceutical Sciences, Atlanta meeting, November 1975.
Supported by Public Health Service Research Grant OH-00518 from the National Institute of Occupational Safety and Health.
[x] To whom inquiries should be directed.

Disposition of Sulfonamides in Food-Producing Animals IV: Pharmacokinetics of Sulfamethazine in Cattle following Administration of an Intravenous Dose and Three Oral Dosage Forms

RICHARD F. BEVILL [*x], LEWIS W. DITTERT [‡], and DAVID W. A. BOURNE [‡]

Abstract □ The plasma and urine data obtained following intravenous administration of sulfamethazine to cattle were fit to a one-compartment pharmacokinetic model with a half-life of elimination of 9 hr and a volume of distribution of 0.35 liter/kg. Sulfamethazine was eliminated by excretion of unchanged sulfamethazine (18%) into urine and by formation of three metabolites subsequently excreted into urine. Sulfamethazine also was administered as a solution, a rapid-release bolus, and a sustained-release bolus. The change in the urinary metabolic pattern with different routes of administration suggested that first-pass metabolism was occurring during the absorption process. The absorption half-life was 6 hr. The absorption process for the two solid boluses kinetically appeared to include a dissolution step.

Keyphrases □ Sulfamethazine—absorption, metabolism, and excretion, various dosage forms compared, cattle □ Sulfonamides—sulfamethazine, absorption, metabolism, and excretion, various dosage forms compared, cattle □ Absorption—sulfamethazine, various dosage forms compared, cattle □ Metabolism—sulfamethazine, various dosage forms compared, cattle □ Excretion—sulfamethazine, various dosage forms compared, cattle □ Pharmacokinetics—sulfamethazine, various dosage forms compared, cattle □ Antibacterials—sulfamethazine, absorption, metabolism, and excretion, various dosage forms compared, cattle

Sulfamethazine is used extensively in veterinary medicine for the treatment of various infections in food-producing animals. Commercially available oral dosage forms for large animals include a solution, a bolus of the sodium salt, and a sustained-release bolus of the free acid. The comparative bioavailabilities and plasma concentration–time profiles of these dosage forms in large animals have not been reported.

The present study investigated the rate and extent of sulfamethazine absorption from three oral dosage forms compared with an intravenous solution of sulfamethazine sodium in 1-year-old cross-bred heifer feeder calves.

EXPERIMENTAL

Intravenous Administration—Three Hereford × Angus heifers, 1 year old, were weighed, fitted with urinary retention catheters[1] attached to 4-liter plastic collection bottles, and assigned to individual slot-floored metabolism cages 3 days prior to dosing. The weights of Animals 1, 2, and 3 were 235, 226, and 245 kg, respectively. Good quality grass hay and water were provided *ad libitum* during acclimatization and postdosing periods. A concentrate mixture, formulated from shelled corn and linseed meal and containing 12% protein, was limit fed to each animal during the study.

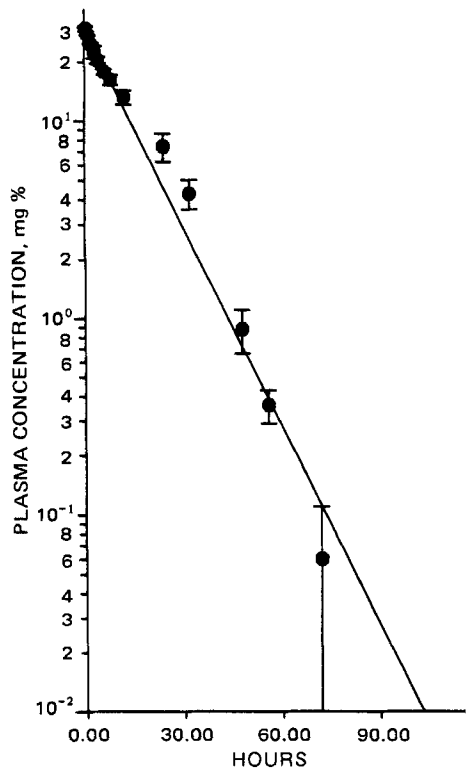


Figure 1—*Semilog plot of average plasma sulfamethazine concentration* (±SD) versus *time following intravenous administration of sulfamethazine sodium (107 mg/kg) to three calves. Points were experimentally observed, and the line was calculated by iterative least-squares fitting to a one-compartment model* ($t_{1/2}$ = *9 hr*, V_D = *0.35 liter/kg*).

A dose of 107 mg/kg (¾ gr/lb) of sulfamethazine as a 12.5% solution of sulfamethazine sodium[2] was rapidly injected *via* the right jugular vein in each animal. All blood specimens were collected from the left jugular vein by serial venipuncture using disposable plastic syringes prerinsed with a 1% solution of heparin sodium in normal saline.

Blood and urine specimens were collected at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 32, 48, 56, and 72 hr following drug administration. The volume of urine collected over each interval was recorded, and a clean collection

[1] Bardex, 24 Fr, C. R. Bard Inc., Murray Hill, N.J.

[2] Prepared by diluting sulfamethazine sodium, 25% (American Cyanamid Co.), with an equal volume of sterile distilled water.

Table I—Average Plasma Sulfamethazine Concentration in Three Calves following Intravenous Administration of 107 mg/kg (3/4 gr/lb) of Sulfamethazine Sodium

Hours	Concentration, mg %
0.5	29.66
1.0	27.35
2.0	24.64
3.0	22.53
4.0	20.46
6.0	17.80
8.0	16.20
12.0	13.20
24.0	7.40
32.0	4.30
48.0	0.88
56.0	0.36
72.0	0.06

bottle was substituted at each collection time. Urine specimens were stored in plastic bottles at −10° until assayed. Within 1 hr of collection, the blood specimens were centrifuged at 3000 rpm for 10 min; plasma was harvested and stored in screw-capped glass tubes at −10° until assayed. All assays were completed within 1 week of specimen collection.

Oral Solution Administration—The three calves were allowed to rest for 21 days between the intravenous and oral solution administrations. Three days prior to dosing, they were reweighed (1 = 232 kg, 2 = 232 kg, and 3 = 250 kg), refitted with urinary retention catheters, and reassigned to individual metabolism cages. The animals were fed and watered as previously described, except that hay and grain were withheld for 24 hr prior to drug administration to avoid regurgitation of the rumen contents and drug during the dosing procedure.

A dose of 107 mg/kg (¾ gr/lb) of sulfamethazine as a 12.5% solution of sulfamethazine sodium was administered to each animal *via* a stomach tube.

Plasma and urine specimens were collected, stored, and assayed as previously described at 0, 1, 4, 5, 7, 9, 12, 24, 32, 48, 56, 72, 96, 120, and 140 hr following drug administration.

Oral Rapid-Release Bolus Administration—The three calves were allowed to rest for 30 days between oral solution and oral bolus administrations. Three days prior to dosing, they were reweighed (1 = 255 kg, 2 = 264 kg, and 3 = 273 kg), refitted with urinary retention catheters, and reassigned to individual metabolism cages. The animals were fed and watered as described for the oral solution administration.

Two boluses[3] containing a total of 30 g of sulfamethazine sodium (27.8 g of sulfamethazine) were administered to each animal using a balling gun. The dose was similar on a milligram per kilogram basis to the dose used in the intravenous and oral solution studies. Slight variations in the milligram per kilogram doses for each animal were tolerated so that intact boluses could be administered.

Plasma and urine specimens were collected, stored, and assayed as previously described at 0, 1, 2, 3, 4, 6, 8, 12, 24, 32, 48, 56, 72, 80, 96, 104, 120, and 144 hr following drug administration.

Oral Sustained-Release Bolus Administration—The three calves were allowed to rest for 30 days between oral rapid-release bolus and oral sustained-release bolus administrations. Three days prior to dosing, they were reweighed (1 = 255 kg, 2 = 268 kg, and 3 = 289 kg), refitted with urinary retention catheters, and reassigned to individual metabolism cages. The animals were fed and watered as described for the oral solution administration.

Three sustained-release boluses[4] containing a total of 67.5 g of sulfamethazine were administered to each animal using a balling gun. The 67.5-g dose was higher than the doses used in the other studies so as to produce comparable plasma sulfamethazine levels. Slight variations in the milligram per kilogram doses for each animal were tolerated so that intact boluses could be administered.

Plasma and urine specimens were collected, stored, and assayed as previously described at 0, 1, 3, 5, 7, 9, 12, 15, 24, 30, 36, 48, 60, 72, 84, 96, 108, 120, 144, and 168 hr following drug administration.

Analytical Methods—All assays were carried out using the methods described previously (1).

Table II—Average Plasma Sulfamethazine Concentration in Three Calves following Oral Administration of 107 mg/kg (3/4 gr/lb) of Sulfamethazine as a Solution of the Sodium Salt

Hours	Concentration, mg %
1.0	4.82
4.0	11.31
5.0	12.38
7.0	12.92
9.0	13.04
12.0	12.80
24.0	9.69
32.0	6.82
48.0	2.53
56.0	1.25

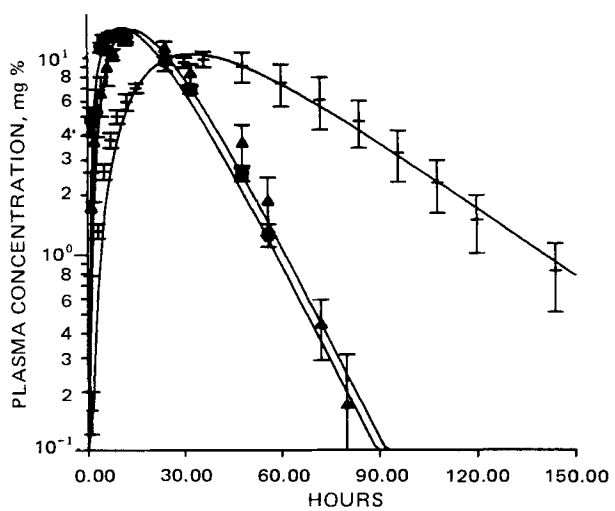


Figure 2—*Semilog plot of average plasma sulfamethazine concentration* (±SD) versus *time following oral administration of sulfamethazine in solution (107 mg/kg)* (●), *in a rapid-release bolus (27.8 g)* (▲), *and in a sustained-release bolus (67.5 g)* (+) *to three calves. Points were experimentally observed, and lines were calculated according to Schemes I and III.*

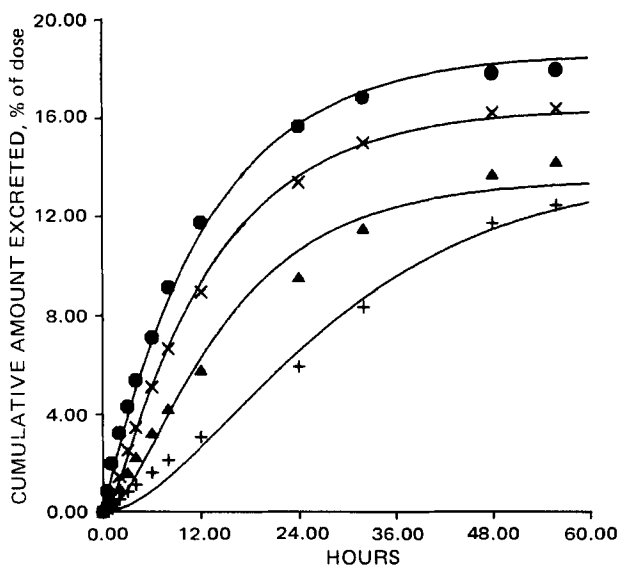


Figure 3—*Plot of average cumulative amount of unchanged sulfamethazine* (●) *and its polar* (▲), *hydroxy* (+), *and acetyl* (×) *metabolites excreted in urine* versus *time following intravenous administration of sulfamethazine sodium (107 mg/kg) to three calves. Points were experimentally observed, and lines were calculated according to Scheme I.*

[3] American Cyanamid Co.

[4] Spanbolets, Norden Laboratories.

Table III—Average Plasma Sulfamethazine Concentration in Three Calves following Oral Administration of 27.8 g of Sulfamethazine as a Rapid-Release Bolus of the Sodium Salt

Hours	Concentration, mg %
1.0	1.69
2.0	3.67
3.0	5.40
4.0	6.50
6.0	8.80
8.0	10.40
12.0	12.40
24.0	11.10
32.0	8.20
48.0	3.63
56.0	1.83
72.0	0.44
80.0	0.17

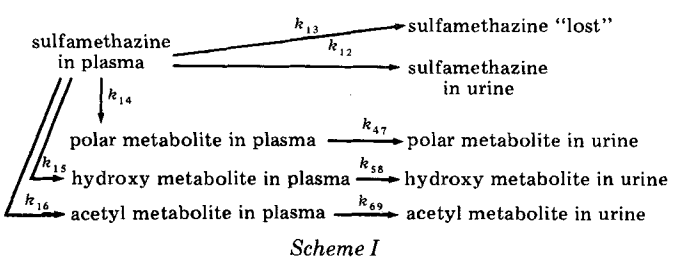
RESULTS AND DISCUSSION

Average plasma sulfamethazine concentrations following intravenous administration of 107-mg/kg doses of sulfamethazine to calves are presented in Table I and plotted in Fig. 1. Average plasma sulfamethazine concentrations following oral administration of a solution of sulfamethazine sodium, a rapid-release bolus of sulfamethazine sodium, and a sustained-release bolus of sulfamethazine are presented in Tables II, III, and IV, respectively, and plotted in Fig. 2. The cumulative amounts of sulfamethazine and its metabolites excreted in urine following the intravenous and oral administrations of sulfamethazine are presented in Tables V–VIII and plotted in Figs. 3 and 4.

The plasma sulfamethazine *versus* time curve obtained following intravenous administration (Fig. 1) appears to be monoexponential, suggesting that a one-compartment pharmacokinetic model is sufficient to describe the time course of sulfamethazine in cattle. Analysis of urine following sulfamethazine administration indicated the presence of unchanged sulfamethazine and three metabolites: the acetyl and hydroxy derivatives and a polar metabolite[5]. If the formations of all three metabolites in plasma are assumed to follow first-order kinetics and the eliminations of sulfamethazine and the three metabolites from plasma are assumed to follow first-order kinetics, Scheme I describes the time course of sulfamethazine and its metabolites in the plasma and urine of cattle.

The value of the overall elimination rate constant, $k_{el} = k_{12} + k_{13} + k_{14} + k_{15} + k_{16} = 0.0774\ hr^{-1}$, was calculated by weighted iterative least-squares fitting (2) to the plasma concentration–time data obtained following intravenous administration. This calculation also estimated a volume of distribution of 0.35 liter/kg. Values of the individual rate constants, k_{12}, k_{13}, k_{14}, k_{15}, and k_{16}, were estimated from the value of k_{el} and the ratios of the total amounts of unchanged sulfamethazine and the three metabolites excreted in urine over the 0–72-hr period after drug administration. Values of the rate constants for the elimination of the metabolites, acetyl (k_{69}), hydroxy (k_{58}), and polar (k_{47}), were estimated from the urinary excretion data for these metabolites.

With all of these values as initial estimates, a least-squares fit of the model shown in Scheme I to the urine–time data for unchanged sulfamethazine and the metabolites (Table V) was obtained using the SAAM 23 program (2) and a digital computer[6]. The final calculated values ($\pm SD$) for the parameters of Scheme I are shown in Table IX. These values were used to generate the calculated lines in Figs. 1 and 3. The good fits of the calculated lines to the experimental data points suggest that the one-compartment pharmacokinetic model is sufficient to describe the disposition and elimination of sulfamethazine in cattle and that the formations and eliminations of the metabolites are first-order processes at the dosage levels studied. The one-compartment model shown in Scheme I and the final calculated parameter values shown in Table IX were subsequently used in analyzing the results obtained following oral administrations.



Scheme I

[5] Determination of the exact structures of the hydroxy and polar metabolites will be the subject of a future publication.

[6] IBM 360/60.

Table IV—Average Plasma Sulfamethazine Concentration in Three Calves following Oral Administration of 67.5 g of Sulfamethazine as a Sustained-Release Bolus

Hours	Concentration, mg %
1.0	0.16
3.0	1.31
5.0	2.63
7.0	3.80
9.0	5.02
12.0	5.95
15.0	7.01
24.0	9.33
30.0	9.43
36.0	9.80
48.0	9.00
60.0	7.41
72.0	6.06
84.0	4.70
96.0	3.26
108.0	2.29
120.0	1.49
144.0	0.82

The relative absorptions of the oral dosage forms of sulfamethazine (Table X) were calculated by comparing the total amount of drug (unchanged drug plus metabolites) excreted in urine following oral administration with the total amount excreted following intravenous administration. The results suggest that the oral solution and the oral rapid-release bolus are relatively efficiently absorbed but that the oral sustained-release bolus is not. This calculation does not take into account that there may be relatively more metabolism following oral administration of any dosage form compared with intravenous administration as a result of greater exposure of the drug to the enzymes of the gut and liver.

A more accurate estimate of the therapeutic potential of the various oral dosage forms is given by their systemic availabilities (3), which were calculated by comparing the total amount of unchanged drug excreted in urine following oral administration with that following intravenous administration (Table X). This calculation measures delivery of active drug to the blood and reflects the different metabolic patterns observed following oral and intravenous administrations. The results suggest that the oral solution and oral rapid-release bolus are relatively efficient at delivering active drug to the blood whereas the oral sustained-release bolus is not. Although the sustained-release bolus does not appear to be an efficient dosage form from the standpoint of relative absorption or systemic availability, inspection of its plasma concentration–time curve (Fig. 2) shows that it maintains plasma concentrations above the mini-

Table V—Average Cumulative Percent of Dose Excreted as Sulfamethazine and Its Metabolites in the Urine of Three Calves following Intravenous Administration of 107 mg/kg (3/4 gr/lb) of Sulfamethazine as the Sodium Salt

Hours	Sulfamethazine	Metabolites		
		Polar	Hydroxy	Acetyl
0.0	0.0	0.0	0.0	0.0
0.5	0.84	0.05	0.06	0.12
1.0	1.98	0.30	0.19	0.56
2.0	3.24	0.88	0.50	1.44
3.0	4.32	1.54	0.82	2.51
4.0	5.39	2.19	1.11	3.46
6.0	7.13	3.19	1.61	5.11
8.0	9.14	4.17	2.12	6.66
12.0	11.77	5.75	3.07	8.95
24.0	15.68	9.49	5.94	13.39
32.0	16.86	11.44	8.35	14.97
48.0	17.84	13.65	11.73	16.22
56.0	17.99	14.16	12.47	16.37

Table VI—Average Cumulative Percent of Dose Excreted as Sulfamethazine and Its Metabolites in the Urine of Three Calves following Oral Administration of 107 mg/kg (3/4 gr/lb) of Sulfamethazine as a Solution of the Sodium Salt

Hours	Sulfamethazine	Metabolites		
		Polar	Hydroxy	Acetyl
0.0	0.0	0.0	0.0	0.0
1.0	0.07	0.02	0.05	0.08
4.0	0.31	0.31	0.32	0.53
5.0	0.72	0.77	0.62	1.32
7.0	1.35	1.33	0.96	2.45
9.0	2.29	1.89	1.36	3.87
12.0	3.65	2.71	1.95	6.00
24.0	8.08	5.80	4.77	15.13
32.0	10.23	7.59	6.89	18.54
48.0	12.61	9.93	10.69	23.09
56.0	13.19	10.66	12.17	24.31
72.0	14.07	11.21	14.24	25.16
96.0	14.45	11.52	15.20	25.44
120.0	14.54	11.71	15.76	25.63

mum therapeutic level (5 mg %) (4) for at least 70 hr. This time is more than twice as long as that with the rapid-release bolus and the solution and probably represents a therapeutic advantage.

The different metabolic patterns of sulfamethazine following intravenous and oral administrations may be seen by comparing Figs. 3 and 4 and Tables V and VI. Figure 3 and Table V show that the major excretion product following intravenous administration was unchanged sulfamethazine, which amounted to 18% of the dose. On the other hand, the major excretion product following administration of the oral solution (Fig. 4 and Table VI) was the acetyl metabolite of sulfamethazine, amounting to more than 25% of the dose. The fraction of the dose excreted as the hydroxy metabolite also increased from 12.5% following intravenous administration to 15.8% following oral administration. Thus, a significant part of the reduction in systemic availability observed with the oral dosage forms of sulfamethazine apparently can be attributed to increased metabolism during movement from the rumen to peripheral plasma.

The kinetics of sulfamethazine absorption following oral administration of sulfamethazine sodium in solution were investigated using the method of Wagner and Nelson (5). The percentage of the dose remaining to be absorbed at each time was calculated from the plasma level data using the value of k_{el} obtained in the intravenous study. A semilog plot of the percent of the dose remaining to be absorbed *versus* time appeared to be linear, indicating that sulfamethazine absorption from solution in cattle is a first-order process with a half-life of about 6 hr (k_a = 0.115 hr^{-1}).

This value of k_a was used as an initial estimate for calculating the final value of the absorption rate constant by least-squares fitting to the plasma concentration *versus* time data using the SAAM 23 program (2).

Table VII—Average Cumulative Percent of Dose Excreted as Sulfamethazine and Its Metabolites in the Urine of Three Calves following Oral Administration of 27.8 g of Sulfamethazine as a Rapid-Release Bolus of the Sodium Salt

Hours	Sulfamethazine	Metabolites		
		Polar	Hydroxy	Acetyl
0.0	0.0	0.0	0.0	0.0
1.0	0.01	0.01	0.01	0.01
2.0	0.08	0.05	0.09	0.08
3.0	0.18	0.22	0.25	0.22
4.0	0.30	0.39	0.40	0.37
6.0	0.52	0.74	0.70	0.75
8.0	0.82	1.24	1.11	1.46
12.0	1.55	2.06	1.76	3.06
24.0	4.80	4.93	4.19	9.26
32.0	6.65	6.65	5.95	12.64
48.0	9.32	9.43	9.36	16.54
56.0	10.00	10.24	10.65	17.53
72.0	10.92	11.61	12.97	18.97
80.0	11.13	11.81	13.39	19.42
96.0	11.32	12.00	13.99	19.95
104.0	11.37	12.05	14.10	20.02

Table VIII—Average Cumulative Percent of Dose Excreted as Sulfamethazine and Its Metabolites in the Urine of Three Calves following Oral Administration of 67.5 g of Sulfamethazine as a Sustained-Release Bolus

Hours	Sulfamethazine	Metabolites		
		Polar	Hydroxy	Acetyl
0.0	0.0	0.0	0.0	0.0
1.0	0.0	0.0	0.0	0.0
3.0	0.02	0.04	0.03	0.02
5.0	0.04	0.12	0.11	0.05
7.0	0.08	0.23	0.22	0.12
9.0	0.13	0.34	0.32	0.22
12.0	0.24	0.55	0.46	0.45
15.0	0.34	0.70	0.58	0.76
24.0	0.98	1.35	1.13	1.89
30.0	1.46	1.76	1.47	2.65
36.0	2.05	2.30	1.94	3.55
48.0	2.97	3.30	2.87	5.25
60.0	3.89	4.29	3.92	6.82
72.0	4.49	5.15	4.84	8.14
84.0	4.97	5.97	5.68	9.19
96.0	5.27	6.54	6.37	9.95
108.0	5.45	7.03	7.04	10.41
120.0	5.58	7.43	7.68	10.75
144.0	5.71	7.85	8.54	11.15
168.0	5.75	8.00	8.88	11.27

The value of the overall elimination rate constant was set equal to the value obtained in the intravenous study. This calculation yielded an absorption rate constant of 0.113 hr^{-1}.

To account for the different metabolic patterns of sulfamethazine following intravenous and oral administrations, a kinetic model was tested where the absorption process consisted of simultaneous transfer of sulfamethazine from solution in the rumen to sulfamethazine in plasma and to the three metabolites in plasma (Scheme II). The remainder of the model, *i.e.*, that describing disposition and elimination of sulfamethazine and its metabolites in plasma, was identical to Scheme I. The values of the rate constants of Scheme I obtained by fitting the plasma and urine data from the intravenous study were used as initial estimates in the least-squares fitting of the oral data.

Initial estimates of $k_{10,1}$, $k_{10,4}$, $k_{10,5}$, and $k_{10,6}$ were calculated by mass balance from the urinary excretion–time data. In fitting the oral data, the following constraints were employed: the value of k_{el} was fixed at the value obtained from the intravenous study, and the value of $k_a = (k_{10,1}$

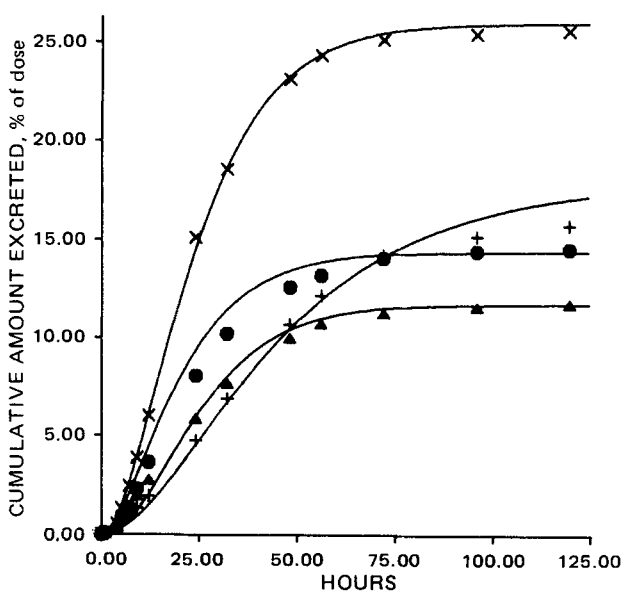
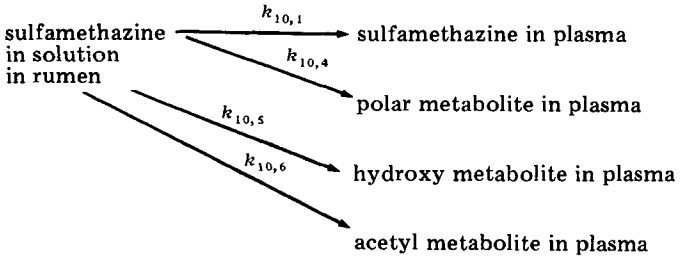
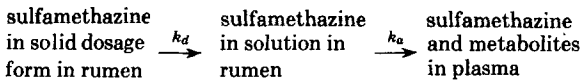


Figure 4—*Plot of average cumulative amount of unchanged sulfamethazine* (●) *and its polar* (▲), *hydroxy* (+), *and acetyl* (×) *metabolites excreted in urine* versus *time following oral administration of sulfamethazine sodium in solution (107 mg/kg) to three calves. Points were experimentally observed, and lines were calculated according to Schemes I and II.*



Scheme II



Scheme III

$+ k_{10,4} + k_{10,5} + k_{10,6}$) was fixed at the value obtained by iterative fitting of the plasma concentration–time data. The values of $k_{10,1}$, $k_{10,4}$, $k_{10,5}$, $k_{10,6}$, k_{47}, k_{58}, and k_{69} were then calculated by least-squares fitting to the data for unchanged sulfamethazine and metabolites in urine (Table VI). The results of this calculation are shown in Table XI. The calculated lines of Fig. 4 were generated using the parameter values in Table XI and appear to fit the experimental points well.

The kinetics of sulfamethazine absorption following administration of the oral rapid-release bolus of sulfamethazine sodium and the oral sustained-release bolus of sulfamethazine were investigated by the method of Wagner and Nelson (5) using the value of k_{el} obtained in the intravenous study. In both cases, the semilog plot of the percent of dose remaining to be absorbed *versus* time appeared to be biexponential. This finding suggested that the absorption process consisted of two successive first-order processes, the initial process being dissolution of the drug and the second process being absorption of the dissolved drug from the rumen (Scheme III).

An estimate of the *in vivo* dissolution rate constant, k_d, was obtained from the semilog plot of percent of dose remaining to be absorbed *versus* time. The value of k_{el} obtained in the intravenous study and the value of k_a obtained in the oral solution study were then used to calculate values for the *in vivo* dissolution rate constants for the rapid-release bolus and the sustained-release bolus by iterative least-squares fitting to the plasma concentration–time data using the SAAM 23 program (2). The values of k_{el}, k_d, and k_a calculated from the plasma data were then fixed; values for $k_{10,1}$, $k_{10,4}$, $k_{10,5}$, $k_{10,6}$, k_{47}, k_{58}, and k_{69} were calculated by least-squares iterative fitting to urine data for unchanged sulfamethazine and its metabolites (Tables VII and VIII). The results of these calculations are shown in Table XI.

The calculated dissolution rate for the sustained-release bolus is much slower than that for the rapid-release bolus. This reduced dissolution rate appears to be effective in reducing the rate of appearance of sulfamethazine in plasma and also in maintaining effective plasma sulfamethazine levels for longer times. Peak plasma levels following administration of the sustained-release bolus were about 75% of those following oral administration of the solution or the rapid-release bolus. The sustained-release bolus, although less efficient (less bioavailable) than the other oral dosage forms (Table X), maintained plasma concentrations of active drug above the minimum effective concentration (5 mg %) (4) for above twice as long as the other dosage forms.

Apparently, a compromise must be considered in designing a "best" oral dosage form of sulfamethazine for cattle. If longer dosing intervals and smoother plasma levels are important factors in sulfamethazine therapy, then the lower bioavailability of the sustained-release dosage form becomes less important than its prolonged release, and this dosage form is preferable. However, if the dosing interval can be shorter and the higher peak plasma levels do not cause increased toxicity, the more completely absorbed rapid-release bolus dosage form (82% relative absorption) may be preferred to either the incompletely absorbed sustained-release dosage form (46%) or the less convenient solution dosage form (99%).

Table IX—Values of the Parameters[a] of the Pharmacokinetic Model (Scheme I) Describing the Metabolism and Excretion of Sulfamethazine in Cattle following Intravenous Administration of 107 mg/kg

Parameter	Value ± *SD*
k_{12}	0.0144 ± 0.0002 hr^{-1}
k_{13}	0.0290 ± 0.0007 hr^{-1}
k_{14}	0.0104 ± 0.0002 hr^{-1}
k_{15}	0.0108 ± 0.0006 hr^{-1}
k_{16}	0.0127 ± 0.0002 hr^{-1}
k_{47}	0.28 ± 0.05 hr^{-1}
k_{58}	0.057 ± 0.009 hr^{-1}
k_{69}	0.9 ± 0.2 hr^{-1}
V_D	0.346 ± 0.002 liter/kg
k_{el}	0.077 ± 0.002 hr^{-1}

[a] Values from SAAM 23.

Table X—Bioavailabilities of Three Oral Dosage Forms of Sulfamethazine Compared with Intravenous Administration

Dosage Form	Relative Absorption	Systemic Availability
Solution	99.2	80.8
Rapid-release bolus	82.2	63.2
Sustained-release bolus	46.4	32.0

Table XI—Values of the Parameters[a] of the Pharmacokinetic Models (Schemes I–III) Describing the Absorption, Metabolism, and Excretion of Sulfamethazine in Cattle following Oral Administration

Parameter	Unit	Solution	Rapid-Release Bolus	Sustained-Release Bolus
k_d	$Hours^{-1}$	—	0.405	0.0261
k_a	$Hours^{-1}$	0.113	0.113[b]	0.113[b]
k_{el}	$Hours^{-1}$	0.077[c]	0.077[c]	0.077[c]
$k_{10,1}$	$Hours^{-1}$	0.0884	0.0808	0.0780
$k_{10,4}$	$Hours^{-1}$	0.00149	0.00619	0.00893
$k_{10,5}$	$Hours^{-1}$	0.00830	0.0119	0.0108
$k_{10,6}$	$Hours^{-1}$	0.0152	0.0145	0.0157
k_{47}	$Hours^{-1}$	0.145	0.0673	0.110
k_{58}	$Hours^{-1}$	0.0298	0.0274	0.0486
k_{69}	$Hours^{-1}$	0.0979	0.0763	0.127
V_D	Liters per kilogram	0.25	0.20	0.13

[a] Values from SAAM 23. [b] Value from oral solution study. [c] Value from intravenous study.

REFERENCES

(1) R. F. Bevill, S. H. Meachum, D. W. A. Bourne, L. W. Dittert, and R. M. Sharma, *Am. J. Vet. Res.*, in press.

(2) M. Berman and M. F. Weiss, "Users Manual for SAAM," National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md., 1968.

(3) M. Gibaldi and D. Perrier, "Pharmacokinetics," Dekker, New York, N.Y., 1975, p. 237.

(4) S. M. Finegold and I. Ziment, in "Antimicrobial Therapy," B. M. Kagan, Ed., Saunders, Philadelphia, Pa., 1970, p. 102.

(5) J. G. Wagner and E. Nelson, *J. Pharm. Sci.*, **53**, 1392 (1964).

ACKNOWLEDGMENTS AND ADDRESSES

Received March 16, 1976, from the *Department of Veterinary Physiology and Pharmacology, College of Veterinary Medicine, University of Illinois, Urbana, IL 61801, and the ‡College of Pharmacy, University of Kentucky, Lexington, KY 40506.

Accepted for publication June 17, 1976.

Presented in part at the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, New Orleans meeting, April 1976.

Supported by Food and Drug Administration Grant 71-69.

* To whom inquiries should be directed.