Bioavailability of Sulfadiazine Solutions, Suspensions, and Tablets in Humans

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Abstract □ A four-way crossover sulfadiazine bioavailability study was conducted in 16 normal healthy male volunteers. The subjects were divided into groups of eight. Each group received four different oral dosage forms of sulfadiazine at 1-week intervals: a solution as a reference, a suspension, and two different tablets. All dosage forms were equivalent to 500 mg of sulfadiazine. Blood samples were obtained at 0, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 25.0, 33.0, and 49.0 hr. Analysis of variance indicated no statistically significant difference ($p > 0.05$) between the dosage forms in terms of area under the plasma level–time curve, peak plasma concentration, and time of peak plasma concentration. In both groups, there were differences between products at isolated sampling times. It was concluded that the four tablet formulations of sulfadiazine exhibited bioavailability characteristics equivalent to those of the solution and the suspension.

Keyphrases □ Sulfadiazine—bioavailability of various dosage forms compared in humans □ Bioavailability—sulfadiazine, various dosage forms compared in humans □ Antibacterials—sulfadiazine, bioavailability of various dosage forms compared in humans

Sulfadiazine, an anti-infective sulfonamide, is used mainly in the treatment of chancroid, trachoma, nocardiosis, and acute urinary tract infections. The drug has an aqueous solubility of less than 0.2 mg/ml (1). Bioavailability differences among sulfadiazine products have been noted (1–5). Sulfadiazine also has appeared on several lists of drugs with potential or actual bioavailability differences (6, 7). In addition, the Food and Drug Administration (FDA) recently implemented a bioequivalence requirement for sulfadiazine tablets (8). In view of the potential for sulfadiazine dosage forms to exhibit bioinequivalence, this study was undertaken to assess the relative bioavailability of currently marketed products.

EXPERIMENTAL

Selection of Products—Four lots of 500-mg sulfadiazine tablets manufactured by different companies met the USP XIX specifications for sulfadiazine tablets[1]. A commercially available suspension containing 500 mg of sulfadiazine/5 ml was employed as a reference product. The suspension was administered with an oral syringe.

A solution of sulfadiazine also was utilized as a reference dosage form. The oral solution was prepared from 10 ml of sulfadiazine sodium (0.25 g/ml) ampuls[2]. A 2.8-ml aliquot was removed from the ampul, equivalent to 500 mg of sulfadiazine, and combined with 20 ml of a chocolate syrup in a 100-ml beaker. The mixture was further diluted with 50 ml of water prior to administration. Care was taken that the entire contents of the beaker were ingested by the subjects.

The individual products are identified in Table I.

Clinical Protocol—Sixteen male volunteers[3] underwent urine analysis and hematological and blood chemistry[4] determinations to ensure that they were in good health. The 16 individuals were divided into groups of eight (Groups I and II). The subjects ranged in age from 20 to 30 years, in weight from 66.8 to 93.2 kg, and in height from 168 to 193 cm. The weight of each subject was within ±10% of the ideal weight for his age, sex, height, and build.

Each subject received a single tablet, suspension dose, or oral solution equivalent to 500 mg of sulfadiazine once a week for 4 weeks. The administration sequence was based on a crossover matrix designed to minimize the influence of any residual or cumulative effects of the preceding doses (9). Each group received two tablet products, the suspension, and the solution. The administration sequence of the drug formulations is presented in Table I.

The subject initially designated as Subject 6 in Group I exhibited signs of an allergic reaction to the first dose of sulfadiazine and was replaced by a new subject. All data reported relative to Subject 6 of Group I concern the subject who replaced the individual experiencing the reaction.

The subjects were given the sulfadiazine products along with 200 ml of water in the morning following an overnight fast. No food or liquid, other than water, was permitted until 4 hr after ingestion. The subjects avoided the use of any other medication during the study.

Blood samples, 10 ml, were collected in heparinized containers at 0, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 25.0, 33.0, and 49.0 hr. The blood samples were centrifuged immediately, and the plasma fraction was removed and frozen until assayed. Aliquots of 2 ml of plasma were assayed in duplicate, using an adaptation of the Bratton–Marshall (10) procedure as previously described (11).

RESULTS AND DISCUSSION

Analysis of variance was used to evaluate statistically significant differences in plasma sulfadiazine levels ($p < 0.05$) at each sampling time. In addition, the time of peak plasma level, peak plasma level, and area under the plasma level–time curve (*AUC*) were subjected to statistical analysis. Where statistically significant differences occurred, the Newman–Keuls *a posteriori* test was used to determine which subjects, treatment sequence, or dosage forms were different ($p < 0.05$).

Plasma Levels at Each Sampling Time—The mean values for plasma sulfadiazine levels at each sampling time for both groups are summarized in Table II and graphically presented in Figs. 1 and 2. In both groups, the plasma levels exhibited considerable variability at each sampling time, with a relative standard deviation generally greater than 20%.

The variability of Product 3 in Group I was greater than that of the

Table I—Experimental Design for Bioavailability Study

Study Group	Subject	Sulfadiazine Products[a] Week 1	Week 2	Week 3	Week 4
I	1, 2	1	2	4	3
I	3, 4	2	3	1	4
I	5, 6	3	4	2	1
I	7, 8	4	1	3	2
II	1, 2	1	2	4	3
II	3, 4	2	3	1	4
II	5, 6	3	4	2	1
II	7, 8	4	1	3	2

[a] Numbers represent product code numbers. Product 1, the oral solution prepared as described in the text, and Product 2, the suspension (Coco-Diazine, 0.5 g/5 ml, lot 0BT91A, Eli Lilly), were common to both groups. The tablet code numbers are as follows: Group I, Product 3, 0.5-g tablets, lot 9SW20A, Eli Lilly; Group I, Product 4, 0.5-g tablets, lot 474206, Lederle Laboratories; Group II, Product 3, 0.5-g tablets, lot 116510, Stanlabs; and Group II, Product 4, 0.5-g tablets, lot 30565, Richlyn Laboratories.

[1] Tablets and data were provided by FDA.
[2] Injection, Lederle Labs, lot 458-151.
[3] Staff and students of the University of Tennessee Center for the Health Sciences. Written informed consent was obtained.
[4] SMA 18/90.

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Table II—Plasma Sulfadiazine Levels at Each Sampling Time [a]

Product [b]	0.5 hr	1 hr	2 hr	3 hr	4 hr	6 hr	8 hr	10 hr	25 hr	33 hr	49 hr
					Group I						
1	15.8	16.9	18.0	17.7	17.3	15.1	12.6	10.8	4.3	2.6	1.0
	(46.6)	(36.2)	(30.6)	(26.5)	(19.0)	(21.1)	(19.1)	(19.3)	(33.5)	(53.0)	(67.9)
2	6.5	9.4	15.3	17.5	17.3	15.1	13.0	11.5	5.0	3.1	1.3
	(59.7)	(44.1)	(21.2)	(13.9)	(17.3)	(15.6)	(15.4)	(17.6)	(32.1)	(50.8)	(81.0)
3	2.5	7.0	11.9	14.5	16.7	16.0	i3.6	11.8	5.3	3.3	1.4
	(138.8)	(104.0)	(58.0)	(37.9)	(30.0)	(25.1)	(23.4)	(24.4)	(34.1)	(50.4)	(70.5)
4	3.0	8.8	13.4	14.8	16.0	15.0	13.1	11.5	4.8	3.0	1.3
	(88.5)	(50.9)	(33.7)	(27.9)	(13.6)	(18.1)	(16.3)	(20.2)	(30.9)	(49.5)	(68.4)
					Group II						
1	14.1	15.4	17.5	18.4	18.3	15.9	13.3	11.3	4.5	2.6	0.9
	(27.3)	(23.2)	(18.1)	(12.4)	(12.3)	(10.2)	(12.3)	(i6.3)	(31.2)	(38.0)	(71.9)
2	7.2	11.3	15.4	17.3	17.2	15.1	13.2	11.3	4.7	2.4	0.9
	(53.0)	(41.7)	(27.1)	(15.8)	(16.8)	(18.4)	(12.5)	(16.7)	(23.7)	(35.8)	(63.8)
3	6.1	11.8	15.6	17.5	17.6	16.7	14.5	12.9	5.7	3.4	1.3
	(67.4)	(48.4)	(35.4)	(22.4)	(20.7)	(19.9)	(25.4)	(27.3)	(43.0)	(50.6)	(66.1)
4	2.5	5.7	11.7	17.0	18.1	17.6	15.0	12.9	5.6	3.2	1.3
	(104.7)	(83.1)	(49.0)	(26.3)	(20.8)	(14.5)	(18.9)	(21.0)	(39.4)	(52.0)	(68.2)

[a] Average data for eight subjects; concentration in micrograms per milliliter; relative standard deviation in percent given in parentheses. [b] See Table I for product code numbers.

Table III—Sulfadiazine Bioavailability Parameters [a]

Product	Peak Plasma Level, μg/ml	Time of Peak Level, hr	$AUC_{(0-49\ hr)}$, μg/ml × hr	$AUC_{(0-\infty)}$, μg/ml × hr	*AUC* Normalized, (μg/ml)(kg/mg)
			Group I		
1	19.3	3.3	317.9	336.6	3.15
	(21.3)	(27.3)	(25.5)	(28.4)	(11.8)
2	17.8	3.9	327.8	354.1	3.11
	(14.7)	(29.1)	(21.1)	(26.7)	(15.4)
3	17.7	3.5	328.5	355.9	3.18
	(28.3)	(68.3)	(24.6)	(28.5)	(21.3)
4	17.4	2.9	314.8	340.4	3.13
	(13.2)	(57.9)	(21.7)	(25.7)	(17.8)
			Group II		
1	19.0	3.0	326.4	342.2	3.31
	(14.4)	(30.9)	(18.6)	(21.6)	(9.3)
2	18.2	3.6	313.2	328.8	3.24
	(17.7)	(53.0)	(17.3)	(19.4)	(10.8)
3	19.0	3.9	358.3	382.0	3.56
	(20.9)	(48.6)	(26.9)	(29.6)	(15:4)
4	18.9	4.5	349.8	373.7	3.49
	(16.0)	(29.1)	(27.7)	(31.1)	(12.0)

[a] Each value is the mean of eight subjects with relative standard deviation given in parentheses.

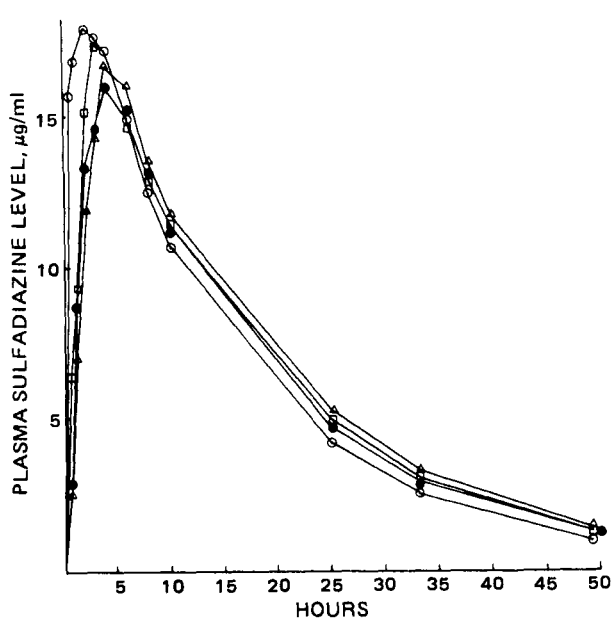

Figure 1—*Mean plasma sulfadiazine levels for Group I. Each data point represents the mean of eight subjects. Key:* ○, *Product 1;* □, *Product 2;* △, *Product 3; and* ●, *Product 4.*

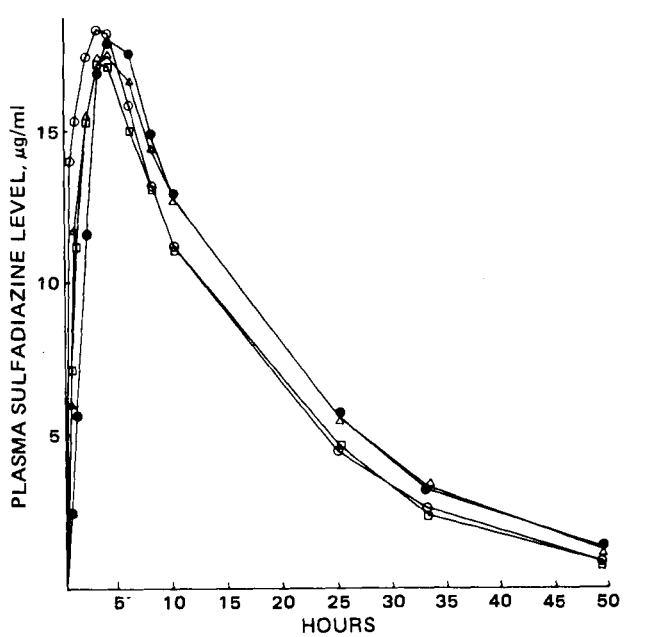

Figure 2—*Mean plasma sulfadiazine levels for Group II. Each data point represents the mean of eight subjects. Key:* ○, *Product 1;* □, *Product 2;* △, *Product 3; and* ●, *Product 4.*

Table IV—Power Analysis Table [a]

Parameter	Minimum Number of Subjects for 20% Difference		Minimum Detectable Difference, %	
	Group I	Group II	Group I	Group II
0.5 hr	≥30	20	54.8	33.3
1.0 hr	≥30	≥30	61.9	45.9
2.0 hr	≥30	20	56.8	34.0
3.0 hr	≥30	10	43.5	24.5
4.0 hr	10	10	23.7	23.4
6.0 hr	8	6	21.4	17.8
8.0 hr	4	4	14.1	16.5
10.0 hr	8	6	20.3	19.2
25.0 hr	4	16	15.0	32.7
33.0 hr	16	16	29.5	32.9
49.0 hr	≥30	≥30	46.8	46.2
Peak plasma concentration, μg/ml	6	8	19.2	20.5
Time of peak plasma concentration, hr	≥30	≥30	63.8	55.4
$AUC_{(0\text{-}49\ hr)}$, μg/ml × hr	4	6	13.6	18.2
$AUC_{(0\text{-}\infty)}$, μg/ml × hr	4	6	12.3	19.7
AUC (normalized), (μg/ml)(kg/mg)	10	6	24.6	19.6

[a] $\alpha = 0.05$, and $\beta = 0.2$.

other tablet (Product 4) in Group I, and both tablet products exhibited greater variability in plasma levels than did the solution (Product 1) or the suspension (Product 2). In the Group II study, one tablet (Product 4) showed greater variability than did the other tablet product (Product 3); both tablet formulations were more variable than either the solution (Product 1) or the suspension (Product 2).

The Newman–Keuls *a posteriori* test indicated significance differences ($p < 0.05$) between products at 0.5 and 1.0 hr for Group I and at 0.5, 1.0, and 2.0 hr for Group II. In the Group I study, the solution (Product 1) exhibited plasma levels greater than those of the other three dosage forms at 0.5 and 1.0 hr. In the Group II study, Product 4 resulted in significantly lower levels at 0.5, 1.0, and 2.0 hr. At 0.5 hr, Product 1 yielded significantly higher drug levels than those of the other dosage forms. At 25 hr, Product 1 exhibited significantly lower plasma levels than those of the other three dosage forms. No other significant differences ($p > 0.05$) between dosage forms were observed at any other sampling time in either the Group I or the Group II study.

Except for the 25-hr sample in the Group I study, there were no significant differences with respect to the sequence of dosage form administration. The Newman–Keuls *a posteriori* test did, however, indicate numerous significant differences at the various sampling times between individual subjects.

Peak Plasma Level, Time of Peak Level, and *AUC*—Table III summarizes the mean peak plasma concentrations, time of peak concentration, and *AUC*.

In both groups, the highest peak concentration was achieved with the solution (Product 1), although there were no statistically significant differences ($p > 0.05$) between the products in either group with respect to this parameter. The time of peak plasma concentration was also not significantly different among the solution, the suspension, and the tablet in either group. The relatively long mean peak level time of 3.0–3.3 hr for the solution may reflect an inherently slow absorption of sulfadiazine, or it may be related to drug precipitation from solution in the acid environment of the stomach. The actual time of peak plasma level may have been overestimated and the magnitude of the peak plasma level may have been underestimated, because the plasma samples were only obtained hourly from 1 to 4 hr after dose administration.

The $AUC_{(0\text{-}49\ hr)}$, computed using the trapezoidal rule, ranged from 314.8 (Product 4) to 328.5 (Product 3) μg/ml × hr in Group I and from 313.2 (Product 2) to 358.3 (Product 3) μg/ml × hr in Group II. In both groups, the $AUC_{(0\text{-}49\ hr)}$ did not differ by more than 13% between any two products. The *AUC* also was computed to time infinity, as previously described (11), and this value was normalized for half-life and a milligram per kilogram dose as suggested by Wagner (12). Neither of these parameters indicated any significant differences between the dosage forms included in either study group.

Biological Half-Life—The apparent half-life, estimated from the terminal slope of a semilog plot of plasma concentration *versus* time, was computed for each dose administered to each subject. In Group I, the mean half-life ranged from 11.1 (*SD* = 2.4) hr for Product 1 to 12.1 (*SD* = 3.3) hr for Product 2. Individual mean subject half-lives, computed for the four formulations, ranged from 9.0 (*SD* = 1.2) to 16.2 (*SD* = 0.9) hr.

In Group II, the mean half-life ranged from 10.0 (*SD* = 3.2) hr for Product 4 to 11.3 (*SD* = 2.9) hr for Product 3. Individual subject half-lives ranged from 9.4 (*SD* = 0.4) to 11.5 (*SD* = 0.9) hr. The observed range of half-lives was similar to previously reported values of 8–17 hr for sulfadiazine (13).

Significant differences were noted between subjects in terms of *AUC*. These differences could be related to the apparent half-life estimated for each subject. The subjects in each group with the lowest $AUC_{(0\text{-}49\ hr)}$ and $AUC_{(0\text{-}\infty)}$ values also exhibited the shortest half-life. Similarly, the subjects with the largest *AUC* values were those with the longest half-life.

Power Analysis—Table IV summarizes the results of the power analysis of the experimental design. The use of eight subjects in each study group was adequate to detect a 20% difference ($p < 0.05$) between formulations in terms of peak plasma concentration, $AUC_{(0\text{-}49\ hr)}$, and $AUC_{(0\text{-}\infty)}$. Because of the variability of the plasma levels at the early sampling times and at the terminal portion of the study, greater than 30 subjects would have been required for differences of this magnitude to be statistically significant at these times.

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