Pharmacokinetic Profile of Sulfisoxazole following Intravenous, Intramuscular, and Oral Administration to Man

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Abstract ☐ A pharmacokinetic profile for sulfisoxazole was defined following the intravenous administration of 2.0-g. single doses to seven human volunteers. The pharmacokinetic profile was determined utilizing a two-compartment open-system model and indicated the following physiological disposition characteristics. The drug distributes from the central compartment rapidly and exhibits a calculated volume of distribution ranging from 13 to 20% of body weight. The drug is eliminated from the body at a fairly rapid rate, with an apparent half-life range of 4.6–6.9 hr. Sulfisoxazole is ultimately eliminated from the body solely by means of urinary excretion, with a mean of 54% of the dose excreted as "free" drug and the remainder as the N_4-acetylated biotransformation product. Following intramuscular and oral administration of the drug, absorption was rapid and complete. Plasma levels peaked by 2 hr. postadministration in most instances, with plasma level maxima ranging from 121 to 210 mcg./ml. The apparent half-lives of elimination of sulfisoxazole from the plasma following intramuscular and oral routes of administration ranged from 5.0 to 7.6 hr. and from 4.6 to 7.8 hr., respectively.

Keyphrases ☐ Sulfisoxazole—pharmacokinetic parameters following intravenous, intramuscular, and oral administration, man ☐ Pharmacokinetics—sulfisoxazole, man ☐ Bioavailability—sulfisoxazole, intramuscular and oral administration, man ☐ Urinary excretion rates—sulfisoxazole following intravenous, intramuscular, and oral administration, man

Sulfisoxazole[1], N^1-(3,4-dimethyl-5-isoxazolyl)sulfanilamide, is a sulfonamide antibacterial agent with a pKa of 5.0 (1). It is indicated in a wide range of acute and chronic urinary tract and soft tissue infections (2–9).

The present study was conducted to define the pharmacokinetic profile of sulfisoxazole in man following intravenous administration and to evaluate the physiological availability of the drug when administered by the intramuscular and oral routes.

METHODS

Protocol—Seven healthy adult male volunteers between the ages of 29 and 45, with no previous history of allergy to sulfonamides, were selected for the study. Each subject received three single 2.0-g. doses of sulfisoxazole 1 week apart by means of the intravenous, intramuscular, and oral routes of administration. The subjects were fasted from 8 hr. prior to dosing until 4 hr. postadministration of the drug.

Six-milliliter blood specimens were collected in heparinized tubes just prior to dosing and at the time intervals indicated in Figs. 1 and 2. The plasma was separated and frozen. The total volume of urine voided was collected at 24-hr. intervals from −24 to 48 hr. postadministration. The volume was recorded and an aliquot was frozen.

The aqueous solubility of sulfisoxazole at 37° was determined as a function of pH between pH 1.3 and 6.6. The dissolution rate of sulfisoxazole was determined at 37°, stirring at 50 r.p.m. in 1 l. and in 5 l. of pH 3 buffer.

Analytical Methods—The plasma and urine specimens were assayed for "free" (direct reacting) and "total" ("free" plus N_4-acetylated) sulfisoxazole by the Bratton–Marshall procedure (10), using an automated assay procedure previously described (11). The samples from the solubility and dissolution studies were analyzed directly by the Bratton–Marshall procedure.

RESULTS AND DISCUSSION

The "free" plasma levels following the intravenous, intramuscular, and oral administration of sulfisoxazole are presented in Table I and Figs. 1 and 2. The corresponding "free" and "total" sulfisoxazole urinary excretion data are presented in Tables II and III.

The pharmacokinetic profile of sulfisoxazole was determined utilizing the data obtained following intravenous administration of the drug. The intravenous blood level curves of all subjects were found to be biexponential. This suggested that the pharmacokinetic evaluation would require minimally a two-compartment open-system model (12). The first exponential is referred to as the fast disposition rate, with a rate constant α, and reflects the distribution of the compound from the central compartment into the body tissues. The second exponential is referred to as the slow disposition rate, or apparent elimination rate, with a rate constant β. Both α and β are hybrid first-order rate constants, each influenced by all of the individual processes involved in the disposition of the drug.

Solution of the differential equations of the two-compartment open model (Scheme I) yields the following integrated equation describing the plasma level-time curve after intravenous administration:

$$(C_p)_t = Ae^{-\alpha t} + Be^{-\beta t} \qquad \text{(Eq. 1)}$$

where $(C_p)_t$ is the concentration of drug in the plasma at time t, and A and B are the ordinate axis intercepts. The individual rate constants of the model, k_{12}, k_{21}, and k_{13}, are calculable from α and β (12).

The pharmacokinetic parameters of sulfisoxazole obtained for the seven subjects following intravenous administration are summarized in Table II. The fast disposition rate constant, α, ranged from 0.67 to 1.74 hr.$^{-1}$ in six of the seven subjects. The plasma level data of the seventh subject did not lend itself to this type of evaluation. These values correspond to an apparent half-life range of 24–62 min. The slow disposition rate constant, β, ranged from 0.10 to 0.15 hr.$^{-1}$, corresponding to an apparent half-life range of 4.6–6.9 hr. The magnitude of the rate constants α and β indicate that sulfisoxazole is distributed and eliminated at a fairly rapid rate.

The individual rate constants k_{12} and k_{21} reflect the rate of distribution into and out of the peripheral compartment from the central compartment. The ratio of k_{21}/k_{12} ranged from 1.4 to 3.0, with a mean of 2.3, indicating that the drug is returning rapidly from distribution sites for elimination from the body. The ratio of β/k_{13} indicates the fraction of drug in the central compartment at
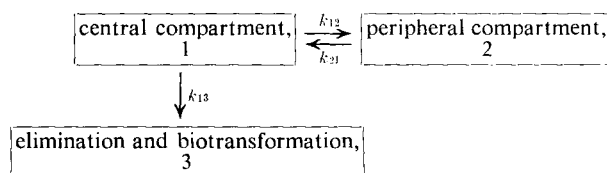
Scheme I

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[1] Sulfisoxazole is the active ingredient in Gantrisin, marketed by Hoffmann-La Roche Inc., Nutley, N. J.

Table I—"Free" Sulfisoxazole Plasma Levels in Man following Intravenous, Intramuscular, and Oral Administration of a 2.0-g. Single Dose

| Subject Number	Route of Administration	0.25	0.50	0.75	1	1.5	2	3	4	6	12	24	48
1	Intravenous	230.5	197.1	184.8	167.3	146.9	137.5	119.5	98.7	78.7	39.6	7.8	3.3
	Intramuscular	—	90.0	—	114.5	139.2	145.0	136.3	132.0	95.7	46.4	17.4	2.9
	Oral	—	98.0	—	123.2	148.0	176.0	140.0	114.8	95.0	50.4	19.6	2.8
2	Intravenous	177.3	175.1	140.8	145.2	110.0	110.0	95.9	84.9	67.3	30.8	13.2	2.7
	Intramuscular	—	98.1	—	132.2	134.9	135.4	121.3	113.1	94.0	53.7	20.4	1.4
	Oral	—	159.9	—	184.1	162.4	147.9	124.7	105.0	87.0	43.5	11.6	Nil[a]
3	Intravenous	181.7	171.6	158.4	150.0	136.4	117.9	101.2	88.0	66.0	32.0	13.2	2.7
	Intramuscular	—	97.0	—	114.3	118.8	121.3	118.8	112.5	86.3	48.8	15.0	2.5
	Oral	—	32.5	—	36.4	41.6	44.2	127.4	127.4	98.8	48.1	16.9	2.5
4	Intravenous	233.2	202.4	188.3	173.8	158.8	145.2	123.2	109.1	79.2	35.0	8.8	4.1
	Intramuscular	—	89.3	—	130.5	136.8	151.8	149.3	135.5	111.8	51.8	18.8	3.5
	Oral	—	15.6	—	23.4	37.7	93.6	89.7	210.6	139.1	67.6	23.4	2.6
5	Intravenous	215.6	189.2	176.0	162.8	138.6	121.0	101.2	88.0	61.6	22.0	4.4	Nil
	Intramuscular	—	106.3	—	129.3	139.3	131.8	125.5	106.8	79.3	30.5	6.8	0.5
	Oral	—	5.8	—	11.6	87.0	136.3	137.7	134.9	95.7	43.1	11.6	Nil
6	Intravenous	204.1	198.3	191.4	181.2	164.8	153.0	123.2	109.8	76.3	39.2	11.8	2.8
	Intramuscular	—	71.8	—	98.0	115.5	125.5	126.8	128.0	105.5	60.5	20.5	4.3
	Oral	—	116.0	—	136.3	159.3	159.5	135.7	121.8	87.0	49.3	17.4	2.9
7	Intravenous	219.7	188.5	180.7	171.4	157.1	148.1	110.5	79.2	70.4	30.0	8.8	1.4
	Intramuscular	—	188.3	—	180.8	169.5	158.3	138.3	122.0	89.5	38.3	13.3	2.0
	Oral	—	46.4	--	113.1	179.8	185.6	162.4	136.3	92.8	90.0	49.3	1.7

[a] Nil is < 0.5 mcg./ml.

Table II—Pharmacokinetic Parameters in Man following the Intravenous Administration of a 2.0-g. Single Dose of Sulfisoxazole

	Subject Number 1	2	3	4	5	6[e]	7	Mean	±SE
A, mcg./ml.	95.92	94.42	69.63	84.60	83.50	—	222.49	108.43	23.13
B, mcg./ml.	175.0	124.20	129.10	181.21	156.2	161.30	137.93	152.13	8.43
C_p^0, mcg./ml.	270.92	218.62	198.73	265.81	239.70	—	360.42	259.03	23.17
α, hr.$^{-1}$	1.73	1.52	0.67	1.74	1.06	—	1.64	1.393	0.18
$0.693/\alpha$, min.[a]	24.0	27.3	62.1	23.9	39.2	—	25.4	33.6	6.16
β, hr.$^{-1}$	0.13	0.10	0.10	0.13	0.15	0.11	0.12	0.12	0.007
$0.693/\beta$, hr.[a]	5.33	6.93	6.93	5.33	4.62	6.30	5.78	5.89	0.33
Percent V_p[b]	9.2	10.9	10.8	11.0	10.8	—	8.5	10.2	0.43
Percent $(V_d)_\beta$[c]	13.6	18.2	15.5	15.6	15.4	—	19.9	16.37	0.93
k_{12}, hr.$^{-1}$	0.50	0.54	0.16	0.46	0.25	—	0.78	0.45	0.09
k_{21}, hr.$^{-1}$	1.16	0.91	0.47	1.23	0.74	—	0.70	0.87	0.12
k_{13}, hr.$^{-1}$	0.19	0.17	0.14	0.18	0.21	—	0.28	0.195	0.02
$Fc = \beta/k_{13}$[d]	0.68	0.59	0.71	0.72	0.71	—	0.55	0.66	0.03
Percent of dose in 0–48-hr. urine as "free" sulfisoxazole	62.8	58.2	38.9	46.3	51.0	48.2	65.2	52.9	3.59
Percent of dose in 0–48-hr. urine as "total" sulfisoxazole	103.1	104.0	72.3	76.4	95.1	81.3	108.1	91.5	5.52

[a] 0.693/constant = half-life. [b] Volume of central compartment as percent body weight. [c] Volume of distribution as percent body weight. [d] Fc = fraction of dose in central compartment. [e] Data did not lend itself to calculation of A and α.

any time that is available for elimination. This fraction ranged from 0.55 to 0.72 in the subjects, with a mean of 0.66, indicating that approximately two-thirds of the drug in the body would be in the central compartment available for elimination.

The volume of the central compartment, V_p, ranged from 9.2 to 11.3% of body weight, whereas the total volume of distribution, $(V_d)_\beta$ (13), ranged from 13.6 to 19.9% of body weight. These values reflect the high affinity of sulfisoxazole for plasma protein (14–17).
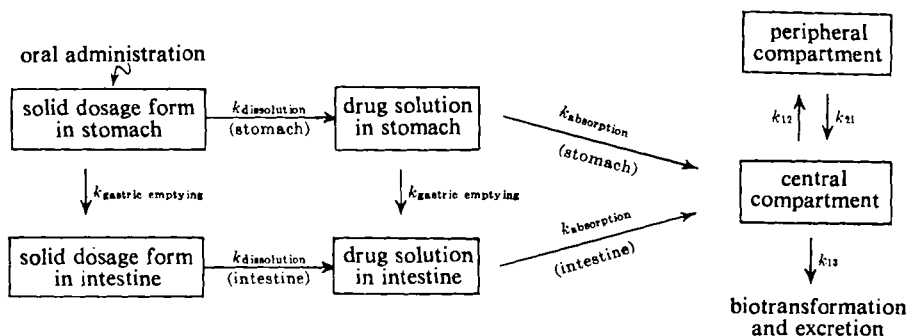
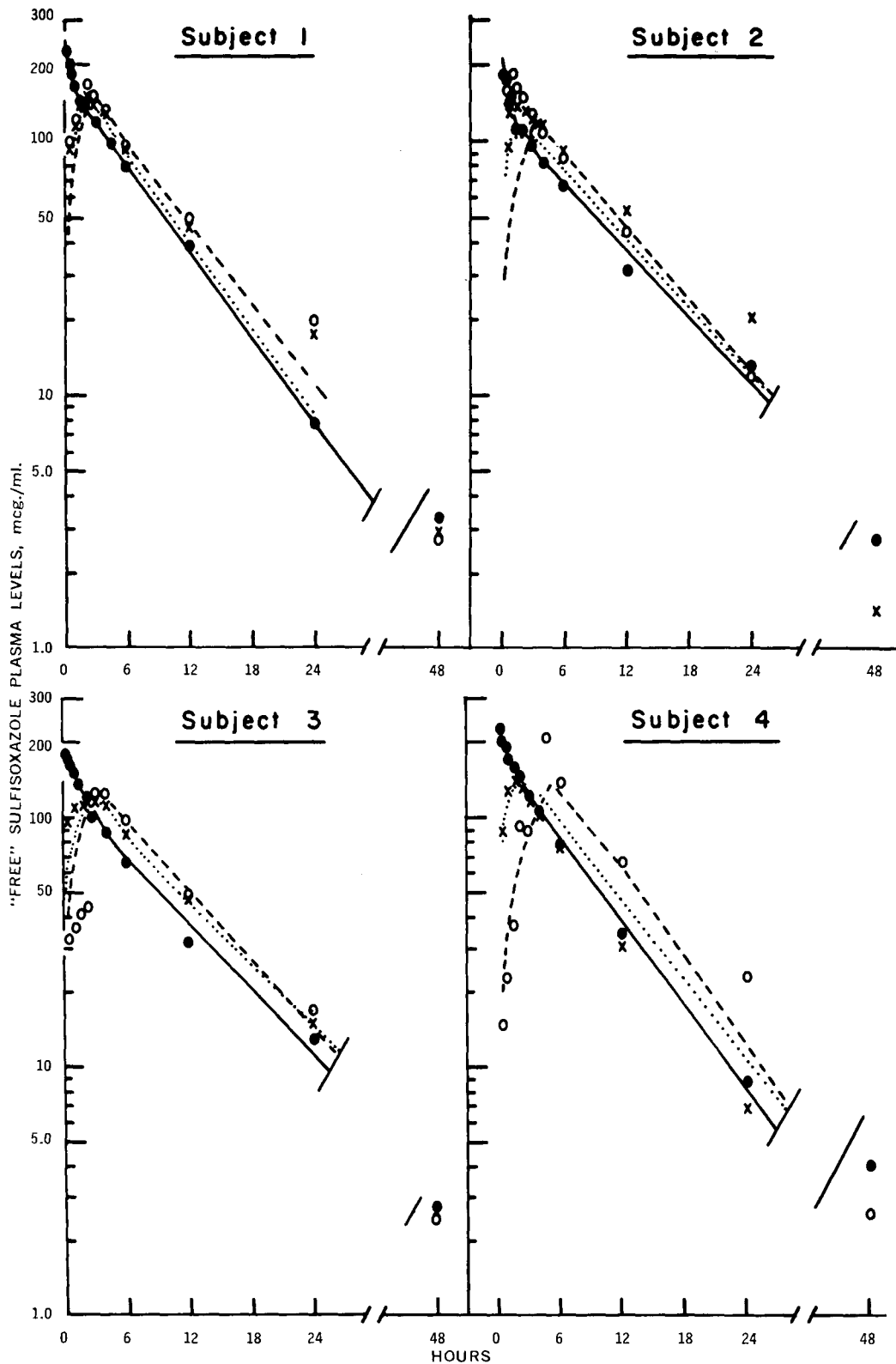*Scheme II—Oral absorption scheme for sulfisoxazole tablets*

Figure 1—*Simulated "free" sulfisoxazole plasma level curves (actual data points) following the intravenous* (●—●), *intramuscular* (X · · · X), *and oral* (O- - -O) *administration of single 2.0-g. doses to Subjects 1–4.*

The affinity of sulfisoxazole for plasma protein and the proteins' binding capacity for sulfisoxazole, *i.e.*, the α and β constants of the Langmuir adsorption isotherm, were reported previously (1). The extent of protein binding of sulfisoxazole is essentially constant over the concentration range studied (1). In light of this constancy

of protein binding, protein binding itself does not affect or alter the overall pharmacokinetic evaluation.

The pharmacokinetic parameters associated with the intramuscular and oral administration of sulfisoxazole are presented in Table III. The absorption of sulfisoxazole following intramuscular and
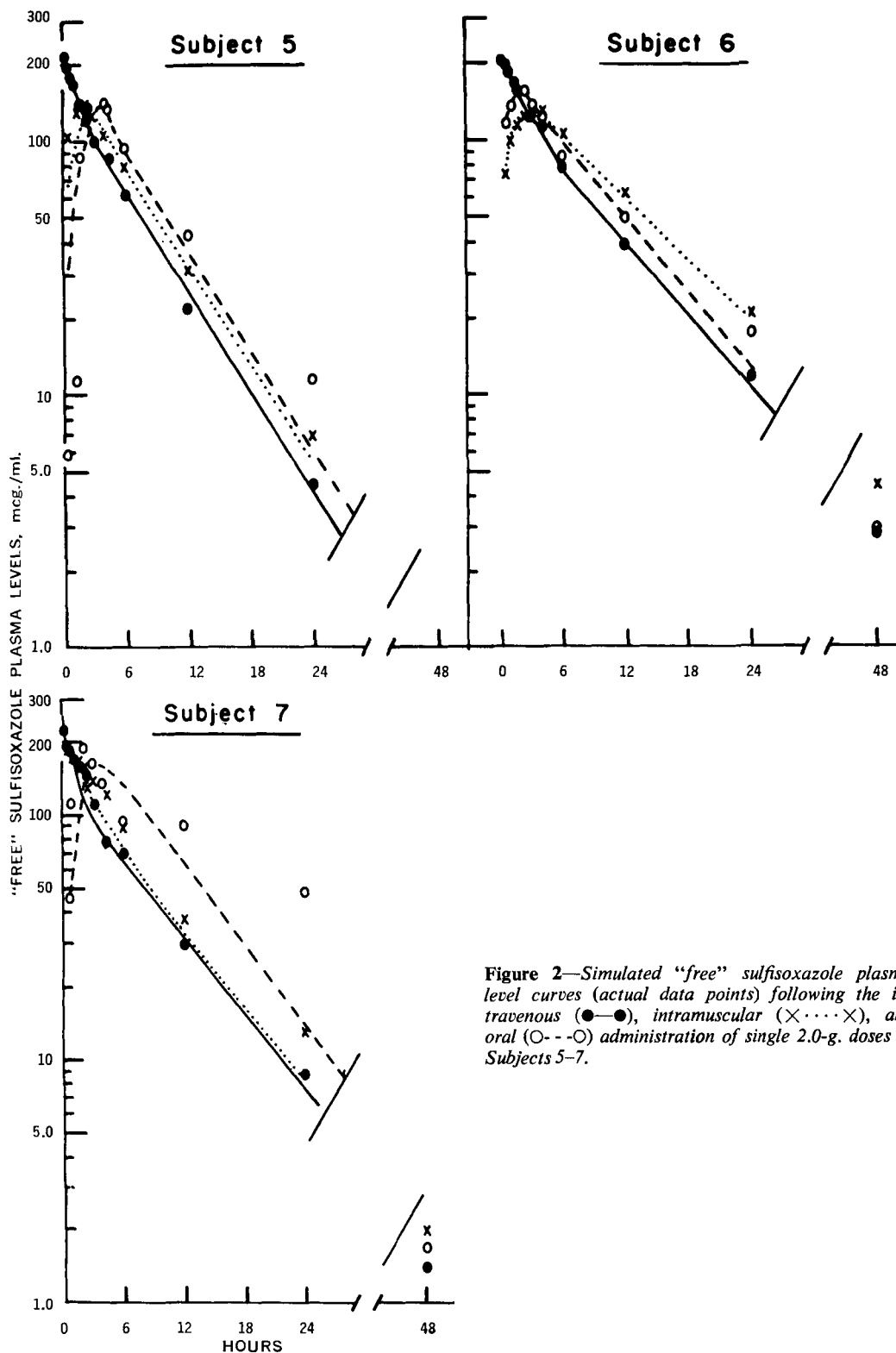
Figure 2—Simulated "free" sulfisoxazole plasma level curves (actual data points) following the intravenous (●—●), intramuscular (X····X), and oral (O- - -O) administration of single 2.0-g. doses to Subjects 5-7.

oral administration of the drug appeared to be equally rapid and essentially complete. Following 10 of the 14 administrations (combined oral and intramuscular data), the plasma levels peaked at 2 hr. postadministration or sooner; following the other four administrations, the levels peaked at 3 and 4 hr. The plasma level maximum following both intramuscular and oral administrations ranged from 121 to 210 mcg./ml. The extent of absorption was determined by comparing the plasma level area ratios, intramuscular/intravenous and oral/intravenous, for each subject. The ratios ranged from 1.03 to 1.3 following intramuscular administration and from 0.94 to 1.3 following intramuscular administration and from 0.94 to 1.3

following oral administration, indicating complete absorption of sulfisoxazole by either route.

Absorption rate constants were calculated for six of the seven subjects following both intramuscular and oral administrations by the method of Loo and Riegelman (18). The intramuscular absorption rate constants presented in Table III were best fit by a first-order function ranging from 0.784 to 2.10 hr.$^{-1}$ in four of the six subjects and by sequential first-order rate constants in the remaining two subjects. The simulated intramuscular plasma level curves presented in Figs. 1 and 2 were in good agreement with the experi-

Table III—Pharmacokinetic Parameters in Man following Intramuscular and Oral Administration of 2.0-g. Single Doses of Sulfisoxazole

	1	2	3	4	5	6[a]	7	Mean	±SE
				Subject Number					
Following intramuscular administration:									
Absorption rate constant, hr.⁻¹	{0.663[b] @1 hr. / 0.989	0.988	{0.633[b] @2.8 hr. / 1.198	0.880	0.784	—	2.10	—	—
0.693/β, hr.[c]	5.59	7.53	7.0	5.78	4.33	7.62	4.95	6.11	0.49
Plasma peak time, hr.	2.0	2.0	2.0	2.0	1.5	4.0	0.5	2.0	0.39
Peak plasma level, mcg./ml.	145.0	135.4	121.3	151.8	139.3	128.0	188.3	144.16	8.30
Plasma level curve area ratio, intramuscular/intravenous	1.14	1.32	1.14	1.20	1.15	1.03	1.05	1.15	0.04
Percent of dose in 0–48-hr. urine as "free" sulfisoxazole	64.0	53.4	60.6	64.4	62.0	59.1	46.3	58.4	2.47
Percent of dose in 0–48-hr. urine as "total" sulfisoxazole	105.8	100.7	102.8	108.3	105.0	104.3	111.4	105.5	1.33
Following oral administration:									
Absorption rate constant, mg./hr.	751.9	998.6	658.9	375.5	568.1	—	655.74	668.12	84.08
0.693/β, hr.[c]	5.78	6.30	6.93	4.95	4.95	7.79	4.62	5.83	0.42
Plasma peak time, hr.	2.0	1.0	3–4	4.0	2–4	1.5–2.0	2	2.5	0.40
Peak plasma level, mcg./ml.	176.0	184.1	127.4	210.6	137.7	159.5	185.6	168.7	11.00
Plasma level curve area ratio, oral/intravenous	1.20	1.15	1.10	1.09	1.31	0.94	1.85	1.23	0.11
Percent of dose in 0–48-hr. urine as "free" sulfisoxazole	58.4	41.5	51.6	54.9	51.0	51.5	52.6	51.6	1.95
Percent of dose in 0–48-hr. urine as "total" sulfisoxazole	104.8	81.1	92.6	103.9	99.3	93.3	104.0	97.0	3.27

[a] Data did not lend itself to absorption rate calculation. [b] Sequential first-order absorption rate constant. [c] 0.693/constant = half-life.

mental data points for five of the six subjects.

The first-order absorption rate constants calculated with the oral plasma level data resulted in poor agreement between the simulated and experimental data points. However, on calculating a zero-order absorption rate constant with the Loo-Riegelman equation, good agreement was obtained between the simulated and experimental oral blood level data (Figs. 1 and 2). A comparison of the simulated oral plasma level curves obtained using either a zero-order or first-order absorption rate constant (presented for Subject 3 in Fig. 3) substantiates the utility of the zero-order absorption rate constant. The calculated zero-order absorption rate constant ranged from 375 to 998 mg./hr. (Table III). Although the oral absorption process is best described by a zero-order function, the oral absorption process *per se* may not necessarily be a zero-order process.

To evaluate the oral absorption process, one must consider Scheme II. The sulfisoxazole tablets must dissolve prior to absorption. The *in vitro* dissolution rate of the drug under sink conditions (19) at the pH range of the stomach is sufficiently rapid to provide drug rapidly for absorption from the stomach. However, the solubility of sulfisoxazole at this pH range is low, as seen on the solubility-pH profile of sulfisoxazole at 37° in Fig. 4. The effect of this low solubility on *in vivo* dissolution and absorption is exaggerated by the large dose administered (2 g.), the small volume of gastric juice in the stomach, and the limited surface area of the stomach. *In vitro* dissolution studies at pH 3, the pH of minimum solubility of sulfisoxazole, were run at 37° in 1 and 5 l. of solution. In both instances the drug levels reached the asymptotic value in 20 min. at 83 and 426 mg. in solution in 1 and 5 l., respectively, or 0.084 mg./ml. Such a dissolution phenomenon would be consistent with limited absorption from the stomach due to the limited volume of gastric fluid available for complete dissolution and the limited surface area of the stomach. This could then result in the accumulation of solid drug in the gastric fluid, with gastric emptying time being a rate-limiting factor. The rate of gastric emptying is highly variable and can be influenced by many physiological factors (20).

A delayed peak blood level of sulfisoxazole from tablets as compared with those from oral solution was observed by Van Petten *et al.* (21) in a study of 10 subjects receiving 4-g. doses of sulfisoxazole tablets and equivalent doses of sodium sulfisoxazole in solution. The sulfisoxazole blood level peaks following oral administration of the solution occurred at, or prior to, 30 min. and were at least 1.3-fold greater than those of the tablet, which exhibited peak levels at 2–3 hr. postadministration. Once the solid drug reached the intestinal tract, the absorption rate would be increased due to the greater solubility of the drug at the pH of the intestinal tract and the greater surface area of the intestinal tract. When sulfisoxa-

zole is administered in solution, problems such as low solubility, limited gastric volume, and gastric emptying time are overcome, resulting in a much faster absorption rate. Therefore, it appears that following oral administration of sulfisoxazole tablets, a hybrid absorption rate constant results which is best described by a zero-order function.

Following both the intramuscular and oral routes of administration, the apparent half-lives of elimination of sulfisoxazole from the plasma were equivalent to those seen following intravenous administration. The apparent half-lives ranged from 5.0 to 7.6 hr. and from 4.6 to 7.8 hr. following intramuscular and oral administrations, respectively. The corresponding range following intravenous administrations was 4.6–6.9 hr.

The percent of dose excreted in the urine as "total" sulfonamide further reflects the extent of absorption of the drug. The mean (range) 0–48-hr. urinary excretion recoveries following intravenous, intramuscular, and oral administrations were 91.5% (72–108), 105.5% (100.7–111.4), and 97.0% (81–104), respectively. These values indicate complete absorption of the administered dose, with elimination exclusively by means of urinary excretion. The mean percent recovery of dose as "free" sulfonamide was 54% of the dose, with a range of 39 to 64%, and reflects large amounts of intact sulfisoxa-
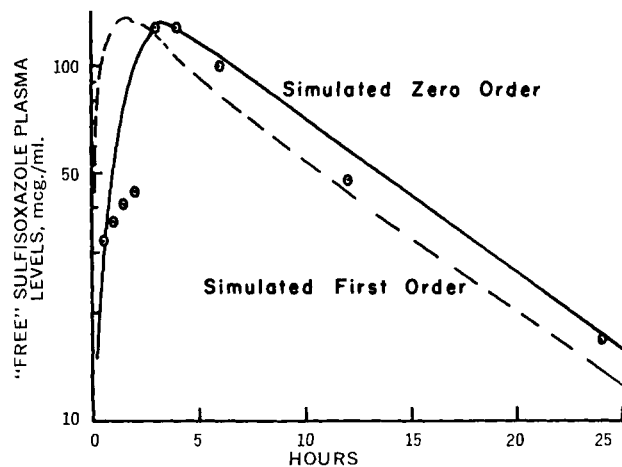

Figure 3—*Simulated oral plasma level curves in Subject 3 obtained using either a zero-order or first-order absorption rate constant.*
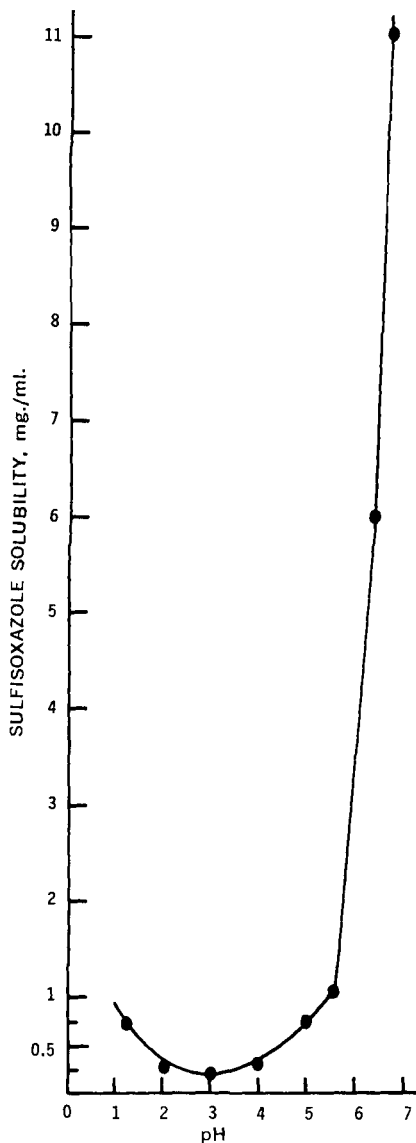
Figure 4—*Solubility of sulfisoxazole at 37° as a function of pH.*

zole in the urinary tract. The urinary excretion data in this study were found to be consistent with those of a previously reported study (22) where the kinetics of sulfisoxazole acetylation and excretion in man were determined following 0.85-g. oral doses. Both studies confirmed the finding of complete absorption, with urinary excretion as the exclusive route of elimination of the administered dose. The apparent half-life of sulfisoxazole elimination determined from the urinary excretion data (22) was within the range reported in Table III, based on blood level determinations.

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