Pharmacokinetic Profile of Trimethoprim in Dog and Man

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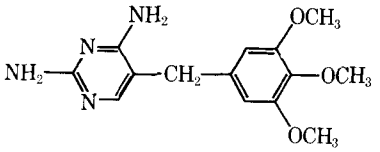
Abstract □ A pharmacokinetic profile of trimethoprim was determined in man and in the dog. The dog was shown to absorb the drug completely, and distribute the drug into the tissues to a great extent. The low recovery of intact trimethoprim in the urine is indicative of biotransformation and/or alternate routes of excretion. The drug is eliminated in man with a half-life of 15–17 hr. In addition, steady-state blood levels were maintained on daily oral dosing over a 13-week period. The dog was shown to eliminate trimethoprim 4 to 5 times faster than man.

Keyphrases □ Trimethoprim—pharmacokinetic profile □ Pharmacokinetics, trimethoprim—man, dog □ Absorption, distribution—trimethoprim □ Fluorometry—analysis

Trimethoprim is an inhibitor of dihydrofolate reductase which potentiates the activity of sulfonamides against a wide variety of bacterial species (1,2).

Chemically, trimethoprim is 2,4-diamino-5-(3′,4′,5′-trimethoxybenzyl)pyrimidine with the following structural formula (Structure I):



Structure I

It is a weak difunctional base with both basic groups titrating almost simultaneously with a pKa of 7.2 (3).

This study was designed to elucidate the physiological disposition of trimethoprim in the dog following i.v. and oral administration and in man following single and chronic oral administration.

EXPERIMENTAL

***In Vivo* Dog Study**—A 5.7-mg./kg. dose of trimethoprim was administered intravenously and orally 2 weeks apart to two different male dogs. Five-milliliter oxalated blood specimens were collected at the time intervals indicated in Table I. The total volumes of urine voided were collected at 24-hr. intervals from 0 to 48 hr. following i.v. administration and from 0 to 72 hr. following oral administration. All specimens were frozen for subsequent analyses.

Human Study—Clinical studies were conducted in two human female subjects.[1] Each subject was given a single oral 200-mg. dose of trimethoprim on Day 1. Repeated oral doses of 50 mg. q.i.d. at 7:00 a.m., 12 noon, 5:00 p.m., and 10:00 p.m. commenced on Day 8 and continued through the 7:00 a.m. dose of Day 22 of the study for Subject R. R. Subject M. H. began the repeated oral dosing of 50 mg. q.i.d. on Day 5 and continued only through the first dose of Day 8.

The dosing, blood, and urine sampling schedules are presented in Table II. Five-milliliter oxalated blood specimens were obtained, the total volume of urine voided was measured, and 50-ml. aliquots were frozen for subsequent analyses.

Table I—Blood and Urinary Excretion Trimethoprim Levels in Two Dogs following the i.v. and Oral Administration of 5.7 mg./kg.

Blood Levels					
i.v., mcg./ml.			Oral, mcg./ml.		
Time	Dog 1	Dog 2	Time	Dog 1	Dog 2
1 min.	5.0	6.6	20 min.	Nil	Nil
2.5	4.7	5.4	40	1.8	0.10
5	3.7	4.6	1 hr.	2.8	0.13
10	3.6	4.5	1.5	2.7	0.18
20	3.0	3.7	2	2.7	1.3
40	2.8	3.4	3	2.1	2.3
1 hr.	2.4	2.8	4	1.8	1.9
1.5	2.2	2.4	6	1.4	1.3
2	1.7	1.9	7.5	1.0	—
3	1.6	1.5	8.0	—	0.8
4	1.3	1.1	11.5	0.3	—
6	1.0	0.7	13	—	0.2
7.5	0.8	0.4	23	Nil	Nil
11	—	0.2	48	Nil	Nil
12	0.3	—	72	Nil	Nil
24	Nil[a]	Nil			
48	Nil	Nil			
55	Nil	—			

Urinary Excretion of Intact Trimethoprim

i.v.			Oral		
Time Interval, hr.	Cum. % of Dose Dog 1	Dog 2	Time Interval, hr.	Cum. % of Dose Dog 1	Dog 2
0–24	16.5	28.4	0–24	11.7	29.9
24–48	18.8	29.0	24–48	14.2	31.9
			48–72	14.5	31.9

[a] Nil is less than 0.1 mcg./ml.

In a separate study, a group of 13 healthy adult male volunteers[2] each received a dose of 50 mg. trimethoprim q.i.d. for 13 weeks. Blood specimens were obtained before and once weekly during drug administration, always at the same time of day with regard to drug administration, just prior to the first dose in the morning, and were frozen for subsequent analysis.

Analytical Methods—Trimethoprim was determined in the blood and urine by a specific spectrofluorometric procedure (4) with a sensitivity of 0.1 mcg./ml.

One-milliliter blood or urine (1 to 10 dilution) specimens were placed in 50-ml. glass-stoppered centrifuge tubes. The specimens were diluted with 7 ml. distilled water and 1 ml. of 1 *N* aqueous sodium carbonate solution. Ten milliliters of chloroform (reagent grade) was added, the tubes stoppered, and extracted gently for 10 min. on a reciprocating shaker. The stoppers were removed and the specimens were then centrifuged at 2000 r.p.m. for 10 min. The aqueous phase was aspirated and the chloroform washed with 5 ml. distilled water. The water was aspirated and an 8-ml. aliquot of the chloroform phase was transferred into a 15-ml. glass-stoppered centrifuge tube. Four milliliters of 0.01 *N* sulfuric acid was then added and the sample extracted by shaking and the phases separated by centrifuging for 10 min. each. A 3-ml. aliquot of the acid phase was placed in a fresh 15-ml. glass-stoppered centrifuge tube to which 1 ml. of a 0.1 *M* potassium permanganate solution in 0.1 *N* sodium hydroxide was added. The solution was mixed, and the test tube was stoppered and heated in a 60° water bath for 20 min. The tubes were cooled to room temperature and 0.1 ml. of a 37% formaldehyde solution (reagent grade) was added. The solution was mixed

[1] The Hoffmann-La Roche Special Treatment Units: one subject at the Newark Beth Israel Hospital under the supervision of Dr. A. Leon and the other subject at Martland Hospital under the direction of Dr. H. Solomon.

[2] The Experimental Therapeutics Unit of Oklahoma State Penitentiary, under the supervision of Dr. J. P. Colmore.

Table II—Trimethoprim Dosing Schedule and Blood Levels in Two Human Subjects Following Single and Chronic Dosing Administration

Day of Study	Hour	Blood Level, mcg./ml. R. R. Dose	R. R. Blood Level	M. H. Dose	M. H. Blood Level
1	0	200 mg.	—[a]	200 mg.	—
	2		2.0		1.4
	4		2.1		1.8
	6		2.0		1.3
	8		1.8		1.2
	12		1.3		1.0
	15		0.9		1.0
2	24		0.7		0.7
	30		0.6		0.7
	36		0.4		0.3
3	48		0.3		0.3
4	72		Nil[b]		Nil
5	96		—	50 mg.	Nil
	98		—	q.i.d.	0.4
	100		—		0.4
	102		—		0.5
	104		—		0.8
	108		—		1.2
6	120		—		1.5
	126		—		1.8
	132		—		1.6
7	144		—		1.5
	156		—		1.8
8	168	50 mg[c]	—		1.6
	170	q.i.d.	0.6		1.9
	172		0.6		1.3
	174		1.2		1.0
	176		1.1		0.9
	178		—		0.9
	180		1.1		0.7
	183		1.4		—
9	192		1.5		—
	198		1.8		—
	204		2.5		—
10	216		2.2		—
11	240		2.3		—
12	264		2.2		—
13	288		2.2		—
14	312		2.2		—
16	360		1.6		—
18	408		2.2		—
21	480		1.8		—
	492		—		—
	495		2.1		—
22	504		—		—
	506		2.5		—
	508		2.8		—
	510		2.3		—
	512		2.1		—
	514	50 mg.	1.8		—
	516		2.3		—
	519	50 mg.	2.2		—
23	528		2.2		—
	534		1.6		—
	540		1.2		—
24	552		0.7		—
25	576		0.3		—
	580		—		—
26	600		Nil		—

[a] —indicates no specimen taken. [b] Nil is below 0.1 mcg./ml. [c] q.i.d. at 7:00 a.m., 12 noon, 5:00 p.m., and 10:00 p.m.

and allowed to stand for 5 min. The solution was acidified by the addition of 1 ml. of 1 *N* sulfuric acid and extracted with 3 ml. of chloroform by shaking, and the phases were separated by centrifuging for 10 min. each. The aqueous phase was aspirated and the chloroform phase transferred to a small test tube.

The fluorescence of the chloroform extract was measured in a 1-cm. path. cell at 345 mμ in a Farrand spectrofluorometer (MK-1) with activation at 295 mμ. Duplicate control specimens of blood or urine and control specimens to which 5 and 10 mcg. of trimethoprim were added as internal standards were carried through the entire procedure. The concentrations in the unknown specimens were calculated on the basis of the internal standard after correction for the control values.

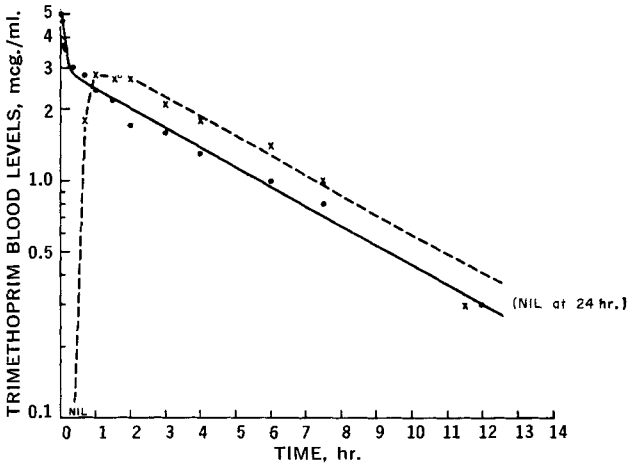


Figure 1—*Trimethoprim blood levels in Dog 1 following i.v. and oral administration. Key: 5.7 mg./kg. trimethoprim to Dog 1:* ●—●, *i.v.; and* ×—×, *oral.*

RESULTS AND DISCUSSION

The dog blood level and urinary excretion data following i.v. and oral administration of trimethoprim are presented in Table I and Figs. 1 and 2. The pharmacokinetic profile of trimethoprim in the dog is summarized in Table III.

The human blood level data of the two subjects receiving both single and chronic administrations of the drug are presented in Table II and Figs. 3 and 4. The corresponding urinary excretion data are presented in Tables IV and V and Fig. 5. The pharmacokinetic profile following the single and chronic oral dosing of trimethoprim is summarized in Table VI. The blood level data of the subjects receiving trimethoprim daily over a 13-week period are presented in Table VII.

Theoretical Considerations—Following the intravenous injection of trimethoprim to two dogs, the resulting blood level curves could be adequately described by the biexponential equations as shown

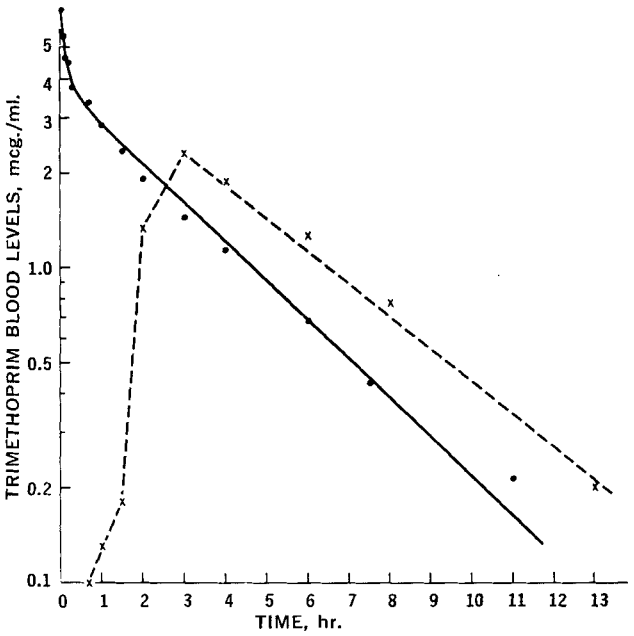


Figure 2—*Trimethoprim blood levels in Dog 2 following i.v. and oral administration. Key: 5.7 mg./kg. trimethoprim to Dog 2:* ●—●, *i.v.; and* ×—×, *oral.*

Table III—Pharmacokinetic Parameters Describing the Physiological Disposition of a 5.7-mg./kg. Dose of Trimethoprim in Two Dogs in Terms of a Two-Compartment Open-System Model

General Equation: $C_p = Ae^{-\alpha t} + Be^{-\beta t}$

Following i.v. Administration	Dog 1	Dog 2
A, mcg./ml.	2.3	3.6
B, mcg./ml.	2.9	3.6
α, hr.$^{-1}$	6.6	13.6
0.693[a]/α, hr.	0.105	0.51
β, hr.$^{-1}$	0.187	0.281
0.693/β, hr.	3.71	2.46
$C_p^0 = A + B$, mcg./ml.	5.2	7.2
Rate Constants		
k_{13}, hr.$^{-1}$	0.327	0.555
0.693/k_{13}, hr.	2.1	1.2
k_{12}, hr.$^{-1}$	2.69	6.46
0.693/k_{12}, hr.	0.26	0.11
k_{21}, hr.$^{-1}$	3.78	6.91
0.693/k_{21}, hr.	0.18	0.10
Volume of Distribution		
V_p, volume of central compartment, l.	8.5	10.9
$(V_D)_{ss}$, total volume of distribution, l.	14.5	21.0
$(V_D)_\beta$, total volume of distribution, l.	14.8	21.5
Total volume as percent of body weight, %	184	154
Following Oral Administration		
β, apparent elimination rate, hr.$^{-1}$	0.224	0.245
0.693/β, hr.	3.1	2.8
Ratio of areas under oral/i.v. blood level curves	1.12	0.94
Estimated percent of dose absorbed[b]	113	112
Absorption Characteristics (Percent of dose absorbed with time)	60% in 40 min. 85% in 1 hr. 100% in 2 hr.	Initial lag period Then 50% in 2 hr. 100% in 3 hr.

Urinary Excretion

Time, hr.	Cumulative Percent of Dose Excreted as Intact Trimethoprim			
	i.v.	Oral	i.v.	Oral
0–24	16.5	11.7	28.4	29.9
24–28	18.8	14.2	29.0	31.8
48–72	—	14.5	—	31.9

[a] 0.693/constant = half-life. [b] Calculated from absorption rate equation (6).

in Figs. 1 and 2. The first portion of the biexponential curve will be referred to as the fast disposition rate, with a rate constant α. The second portion of the curve will be referred to as the slow disposition rate, with a rate constant β. It should be noted that α and β are both hybrid rate constants, each influenced by all the individual processes of the disposition of the drug. The rate constant α reflects the distribution phase of the compound from the central to the peripheral (tissue) compartment. The rate constant β reflects the elimination rate of the drug from the body. The physiological

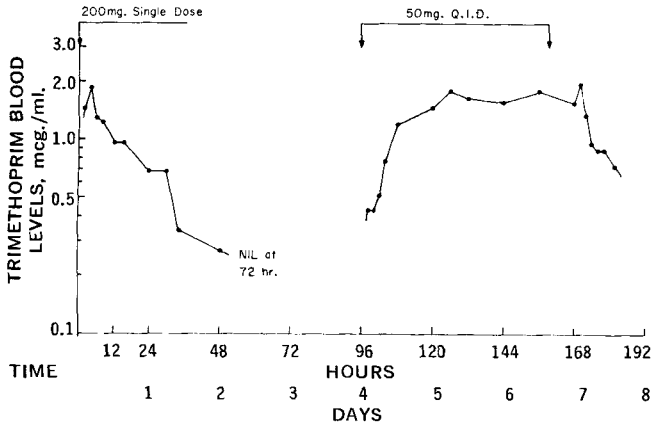


Figure 3—*Trimethoprim blood levels in Subject M. H. following single and chronic oral administration.*

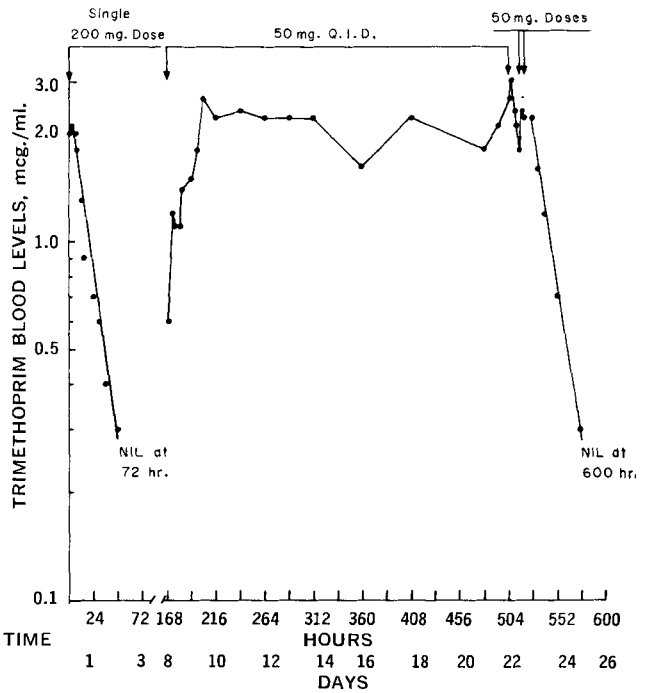
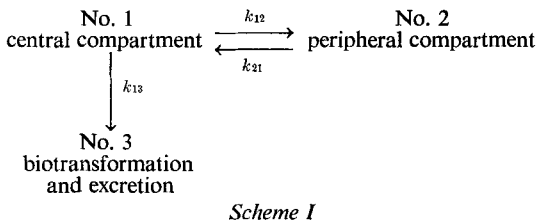


Figure 4—*Trimethoprim blood levels in subject R. R. following single and chronic oral administration.*

Table IV—Urinary Excretion Levels of Intact Trimethoprim in Subject R. R.

Day	Dosing Schedule	Hour Interval	Total mg. Excreted	Percent of Dose Excreted as Intact Drug
1	200-mg. single dose	0–2	0.1	
		2–4	3.5	
		4–6	4.2	
		6–8	8.4	
		8–12	5.1	
		12–15	8.5	
		15–24	12.7	21.3 in 24 hr.
2		24–30	4.1	
		30–36	5.0	
		36–48	12.8	
3		48–72	8.5	
4		72–96	2.2	
5		96–120	0.9	
6		120–144	Nil	
7		144–168	Nil	38.0 of single 200-mg. dose
8	50 mg. q.i.d.	168–170	0.6	
		170–172	1.9	
		172–174	—	
		174–176	4.3	
		176–180	5.9	
		180–183	8.1	
		183–192	14.7	17.8 in 24 hr.
9		192–198	10.7	
		198–204	9.7	
		204–216	31.0	20.4 in 24 hr.
10		216–240	67.0	33.5 in 24 yr.
11		240–264	78.0	39.0 in 24 hr.
12		264–288	63.3	31.7 in 24 hr.
13		288–312	57.3	28.7 in 24 hr.
14		312–336	90.1	45.1 in 24 hr.
15		336–360	69.1	34.6 in 24 hr.
17		384–408	63.0	31.5 in 24 hr.
20		456–480	55.4	27.7 in 24 hr.
22		504–506	4.1	
		506–508	6.0	
		508–510	5.3	
		510–514	7.3	
	50 mg.	514–516	4.3	
		516–519	7.3	
	50 mg.	519–528	22.8	
23		528–534	11.1	
		534–540	10.7	
		540–552	36.7	
24		552–576	23.5	
25		576–600	10.4	
26		600–624	3.1	

disposition of trimethoprim may therefore be defined in terms of the two-compartment open-system model shown in Scheme I (5):



Scheme I

Solution of the differential equations resulting from such a model yields the following integrated equation describing the blood level-time curve after a single intravenous injection as seen in Figs. 1 and 2:

$$C_p = Ae^{-\alpha t} + Be^{-\beta t}$$

where C_p is the concentration of drug in the plasma, and A and B are the ordinate axis intercepts.

The α and β are both hybrid rate constants reflecting all the individual rate processes; however, k_{12}, k_{21}, and k_{13} are individual rate constants calculable from this equation (5). The k_{12} and k_{21} are first-order rate constants of distribution and k_{13} is the sum of the simultaneous processes of biotransformation and excretion, all assumed to be first-order processes. This is the rate constant of the elimination reaction *per se*.

The absorption rate is calculated from the following relationship (6):

$$\left(\frac{A}{V_p}\right)_{tn} = C_{p_{tn}} + k_{13} \int_{t_0}^{tn} C_p\,dt + C_{T_{tn}}$$

which indicates that the amount absorbed per unit volume of distribution (A/V_p) at time tn equals the plasma level $(C_p)_{tn}$ plus the tissue level $(C_T)_{tn}$ plus the amount eliminated $(k_{13} \int_{t_0}^{tn} C_p\,dt)$ at time tn.

In a two-compartment open-system model the total volume of distribution of the entire system $(V_D)_{ss}$, when calculated with reference to the concentration of drug in the central compartment, is the sum of the volume of the central compartment, V_p, and of the peripheral (tissue) compartment, V_T (7), where V_p = administered dose/$A + B$ and $(V_D)_{ss} = V_p\,(k_{12} + k_{21})/(k_{21})$.

The volume of distribution can also be calculated using the equation as presented by Gibaldi *et al.* (8) and is referred to as $(V_D)_\beta$.

In this case, $(V_D)_\beta = V_p/f$ where: $f = C_2/(C_2 + C_2^1)$, $C_2 = B/(A + B)$, and $C_2^1 = k_{12}/(\alpha - \beta)$.

Physiological Disposition of Trimethoprim in the Dog—The pharmacokinetic parameters summarized in Table III indicate that trimethoprim has fast disposition rate constants, α, of 6.6 and 13.6 hr.$^{-1}$, respectively, in Dogs 1 and 2. The slow disposition rate constants, β, were 0.187 and 0.281 hr.$^{-1}$ corresponding to half-

Table V—Urinary Excretion Levels of Intact Trimethoprim in Subject M. H.

Day	Dosing Schedule	Hour Interval	Total mg. Excreted	Percent of Dose Excreted as Intact Drug
1	200-mg. single dose	0–2	1.0	
		2–4	2.9	
		4–6	3.3	
		6–8	1.7	
		8–12	6.2	
		12–15	2.2	
		15–24	10.7	14.0 in 24 hr.
2		24–30	4.9	
		30–36	2.7	
		36–48	8.3	
3		48–72	7.3	
4		72–96	Nil[a]	25.6 of single 200-mg. dose
5	50 mg. q.i.d.	96–98	0.09	
		98–100	0.09	
		100–102	0.3	
		102–104	2.9	
		104–108	2.7	
		108–120	12.0	9.0 in 24 hr.
6		120–126	4.0	
		126–132	6.4	
		132–144	20.7	15.6 in 24 hr.
7		144–168	48.1	24.1 in 24 hr.
8		168–170	4.0	
		170–172	1.1	
		172–174	3.1	
		174–176	4.2	
		176–180	7.4	
		180–183	2.6	
		183–192	8.2	

[a] Nil below 0.1 mcg./ml.

lives of 3.7 and 2.5 hrs, and reflect the apparent elimination rates of the drug from the body.

The volumes of the central compartment, V_p, were calculated to be 8.5 and 10.9 l., respectively. The total volumes of distribution, $(V_D)_{ss}$, of trimethoprim were calculated to be 184 and 154% of body weight in the two dogs, suggesting significant tissue uptake of trimethoprim. $(V_D)_\beta$ was calculated and found to be almost identical with the $(V_D)_{ss}$ calculation (Table III).

Only 18.8% of the intravenously administered dose was recovered as intact drug in the 0 to 48-hr. urine of Dog 1 and 29% in Dog 2, indicating biotransformation and/or alternate routes of excretion. Almost all the recovered trimethoprim was excreted in the urine during the 0 to 24-hr. interval.

The data indicate fairly rapid and complete absorption of the orally administered drug in the dog (Table III) with Dog 2 exhibiting a lag in the start of absorption. Absorption was essentially complete in 2 hr. in Dog 1 and in 3 hr. in Dog 2.

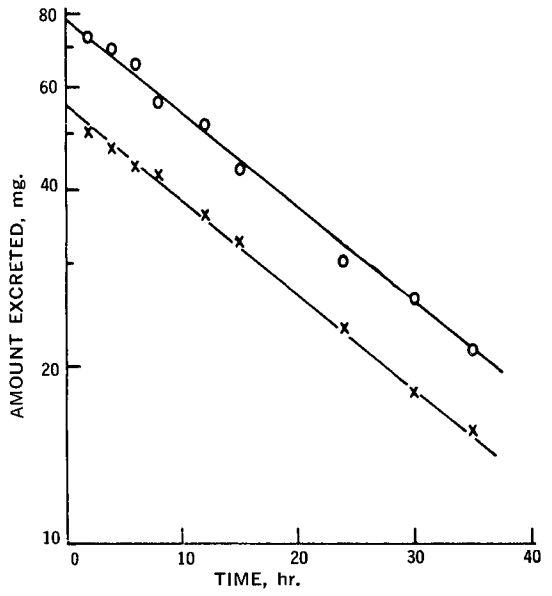


Figure 5—*Urinary excretion of intact trimethoprim in two human subjects. Key:* O—O, *R. R.; and* ×—×, *M. H.*

Physiological Disposition of Trimethoprim in Man—The pharmacokinetic profile following the administration of a single 200-mg. oral dose of trimethoprim to two subjects is presented in Table VI.

In relation to body weight the single doses represented 2.3 mg./kg. for M. H. and 3.4 mg./kg. for R. R.

In each case the blood level curves (Figs. 3 and 4) peaked at 4 hr. postadministration. Subjects R. R. and M. H. exhibited blood level peaks of 1.8 and 2.1 mcg./ml. and elimination rates of 4.0 and 4.6%/hr. corresponding to half-lives of 17.3 and 15 hr., respectively.[4]

Estimates of the volume of distribution following single oral

Table VI—Pharmacokinetic Evaluation of Trimethoprim in Two Human Subjects

	Subject	
	M. H.	R. R.
Single oral dose		
Dose, mg.	200	200
Weight, kg.	87.5	58.9
Dose, mg./kg.	2.29	3.40
Blood level peak		
mcg./ml.	1.84	2.1
Time, hr.	4	4
Elimination rate constant from bloodstream, $hr.^{-1}$	0.040	0.046
Corresponding half-life, hr.	17.3	15.0
Estimated % volume of distribution	158	177
Percent of dose recovered as intact drug in urine	25.6	36.4
Elimination rate constant from urinary excretion of intact trimethoprim, $hr.^{-1}$	0.036	0.037
Corresponding half-life	19.5	18.7
Chronic oral dose of 50 mg. q.i.d.		
Minimum steady-state blood level, mcg./ml.	1.5	2.2
Elimination rate constant following last dose, $hr.^{-1}$	—	0.047
Corresponding half-life, hr.		14.6

Table VII—Mean Trimethoprim Blood Levels[a] following the Daily Administration of 50 mg. q.i.d. to 13 Human Subjects for 13 Weeks

Subject No.	Wt., kg.	[a]Mean ± *SE*
1	86.4	0.867 ± 0.054
2	65.0	1.522 ± 0.047
3	75.9	1.839 ± 0.088
4	100.0	0.325 ± 0.033
5	63.6	1.348 ± 0.077
6	84.5	1.166 ± 0.094
7	99.1	0.558 ± 0.055
8	76.4	1.319 ± 0.099
9	76.8	0.972 ± 0.047
10	75.0	1.138 ± 0.064
11	70.9	0.721 ± 0.066
12	72.7	1.320 ± 0.099
13	70.5	1.420 ± 0.036

[a] Mean of 13 weekly determinations.

doses were made by means of the area equation (9) and are presented in Table VI. It should be noted that $(V_D)_{area}$ has been shown to be mathematically identical to the $(V_D)_\beta$ term previously defined (8):

$$(V_D)_{area} = \frac{\text{amount of drug absorbed}}{\beta(\text{area})}$$

where complete absorption of the dose is assumed, β is the apparent elimination rate constant, and the (area) is the area under a blood level curve from time = 0 to time = ∞. The percent volume of distribution for Subjects M. H. and R. R. were calculated to be 158 and 177% of body weight, indicative of tissue uptake and possible localization of the drug.

The percent of dose excreted as intact drug following oral administration of single 200-mg. doses as seen in Tables IV and V were 25.6 and 36.4% for Subjects M. H. and R. R., with urinary elimination rates of 3.6 and 3.7%/hr. corresponding to half-lives of 19.5 and 18.7 hr. (Fig. 5). The low recovery of the intact drug in the urine is an indication of biotransformation and/or alternate routes of excretion.

Twenty-four-hour urine specimens were collected during the chronic dosing period for the above two subjects and analyzed for intact trimethoprim. The results are presented in Tables IV and V. The daily intact trimethoprim urine levels ranged from 18 to 45% of the administered dose in Subject R. R. and from 9 to 20% in Subject M. H.

Following the chronic administration of 50 mg. trimethoprim q.i.d. (every 5 hr.) to Subjects M. H. and R. R., they exhibited minimum steady-state blood levels of approximately 1.5 and 2.2 mcg./ml., respectively, as indicated in Figs. 3 and 4.

It is interesting to note that the steady-state blood levels are achieved within 2–3 days of chronic administration and that the steady-state levels achieved on dosing 50 mg. q.i.d. (every 5 hr.) are approximately the same as the single dose, 200 mg., peak blood level. Estimated steady-state blood levels were calculated from the elimination rate data utilizing a q.i.d. dosing regimen of every 6 hr. based on the equations of Boxer *et al.* (10). The calculated steady-state minimum–maximum blood levels are 1.7–2.1 mcg./ml. for Subject M. H. and 2.0–2.6 mcg./ml. for Subject R. R. These simulated values are in excellent agreement with the experimental finding indicated above.

The trimethoprim blood levels reported in Table VII following the daily administration of 50 mg. q.i.d. for 13 weeks indicate that steady-state levels were evident by the end of the 1st week of treatment and maintained throughout the experimental period. This finding is substantiated by the small standard error about the mean blood level in each subject which is consistent with steady-state conditions. This would, therefore, preclude drug cumulation or enzyme induction by trimethoprim over a 13-week period.

The mean minimum steady-state trimethoprim blood level of the 13 subjects was 1.1 mcg./ml. with a range from 0.33 to 1.84 mcg./ml. It should be noted that the subjects with the lower blood levels represented those with the higher body weights. The minimum steady-state trimethoprim blood levels seen in the 13-subject study group corresponds with the steady-state blood levels seen in the two-subject study group. In view of these findings one may predict blood levels resulting from multiple dosing, based on pharmacokinetic data obtained from a single dose.

In attempting to compare the disposition profiles of trimethoprim in the dog and in man, it appears that both species absorb the drug well and distribute the drug extensively into the tissues. However, differences are discernible in the rates of elimination of trimethoprim in that the dog eliminated the drug 4–5 times faster than the human Subjects M. H. and R. R.

SUMMARY

1. Trimethoprim appears to be absorbed well and is highly distributed in both the dog and man.

2. In two human subjects the intact drug was eliminated from the bloodstream with half-lives of 15 and 17.3 hr.

3. In man, 50 mg. administered q.i.d. every 5 hr. gives rise to a steady-state blood level approximately the same as the maximum blood level achieved with a single 200-mg. dose.

4. Steady-state blood levels were maintained on daily dosing over a 13-week interval.

5. The low recovery of the intact drug in the urine is indicative of a high degree of biotransformation and/or alternate routes of excretion.

6. The dog eliminated the drug 4 to 5 times faster than the two human subjects studied.

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