ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1979, p. 447-451
0066-4804/79/03-0447/05$02.00/0

Vol. 15, No. 3

Clinical Pharmacology of Intravenously Administered Trimethoprim-Sulfamethoxazole

WILLIAM E. GROSE, GERALD P. BODEY,* AND TI LI LOO

Department of Developmental Therapeutics, The University of Texas System Cancer Center-M. D. Anderson Hospital and Tumor Institute, Houston, Texas 77030

Received for publication 14 April 1978

Pharmacokinetic studies of intravenously administered trimethoprim-sulfamethoxazole (TMP-SMX) were conducted in 11 patients with cancer while they received therapy with this drug combination for infection. Each patient received 160 mg of TMP and 800 mg of SMX every 8 h. The highest plasma concentrations of both agents were attained at the end of a 1-h infusion period, and the levels were maintained above 38 μg of free SMX and 2 μg of TMP per ml for 2 to 4 h on day 1. On day 4, these concentrations were exceeded at all time intervals of blood sampling. High concentrations of TMP and free SMX were recovered in the urine during the 8-h period. The plasma half-lives of TMP and free SMX, as determined during the first 8-h period, were 7.6 and 8.6 h, respectively. Compared with SMX, TMP had an approximately 2.5 times higher volume of distribution. This drug combination was well tolerated by the patients and unaccompanied by drug-related toxicity.

Trimethoprim-sulfamethoxazole (TMP-SMX) is a synergistic antimicrobial combination against a wide spectrum of bacterial pathogens (1 5, 6, 8). It acts by sequentially blocking metabolic pathways in the production of tetrahydrofolate within the microorganism (10). There has been extensive clinical experience attesting to its efficacy in the treatment of localized and systemic infections in humans (7, 18).

Considerable clinical pharmacological and pharmacokinetic data have appeared in the literature on oral TMP-SMX, both in adults and in children (2, 12-14, 10). At our institution, interest in the use of intravenously administered TMP-SMX stemmed from the encouraging results obtained from the oral therapy of systemic infections in cancer patients (7). However, some patients who are unable to tolerate oral medications might also benefit from this medication. During a therapeutic evaluation of intravenous TMP-SMX for proved infections among cancer patients, pharmacokinetic studies were conducted on 11 of them. The results obtained from these studies are included in this report.

MATERIALS AND METHODS

Eleven cancer patients, 5 males and 6 females, with documented infections were the subject of this study. Their median age was 60 years (range, 17 to 78 years), and their median weight was 143 lb (range, 105 to 165 lb). All patients had normal renal function, as measured by urinalysis, blood urea nitrogen (8 to 20 mg/dl), and serum creatinine levels (male 0.9 to 1.5 mg/dl; female 0.8 to 1.2 mg/dl), and normal liver function, as measured by serum glutamic oxaloacetic transaminase (5 to 20 mU/ml) and bilirubin (<1.0 mg/dl). All laboratory studies cited were repeated weekly after the initiation of the study, or on completion if therapy was terminated in less than 1 week. Each of the 11 patients received intravenous therapy with 160 mg of TMP and 800 mg of SMX (Bactrim) given in 200 ml of 5% dextrose solution over 60 min. Doses were repeated at 8-h intervals. Bactrim was supplied by Hoffman-La Roche, Inc., Nutley, N.J., in the form of 5-ml ampoules, each containing 80 mg of TMP and 400 mg of SMX in 40% propylene glycol solution. Blood was sampled at 0, 1, 2, 4, 6, and 8 h, and the urine was collected at 0 h and subsequently at two time intervals of 0 to 4 h and 4 to 8 h. Pharmacological studies were repeated on day 4, but only blood samples were collected. Informed consent was obtained according to institutional policies.

Each blood sample was collected in an oxalate-treated test tube, and the plasma was separated and frozen at −50°C until assayed. The urine samples collected were also kept frozen at the same temperature before processing. Plasma and urine levels of the individual components of TMP-SMX were assayed according to the methods of Schwartz et al. (16) and Bratton and Marshall (3), respectively, by George J. Kavarnos of the Bio-Analytic Laboratories, Norwich, Conn., through the courtesy of Hoffman-La Roche, Inc.

TMP was extracted from plasma or urine at basic pH with chloroform. After back extraction into diluted sulfuric acid, it was oxidized by potassium permanganate to trimethoxybenzoic acid. Excess potassium permanganate and manganese dioxide were removed with formaldehyde. The fluorescence of trimethoxybenzoic

acid in chloroform, as measured by spectrofluorometry, was used to quantitate TMP. Following protein precipitation, plasma SMX was determined by diazotization and coupling with the Bratton-Marshall reagent; the azo dye so generated was measured spectrophotometrically. "Free" SMX, including intact SMX and any metabolite which had an unsubstituted aromatic amino group in position 4, was quantitated directly by this method. "Total" SMX, comprising of "free" plus N^4-acetylated sulfonamide, was determined after alkaline hydrolysis of the sample. The N^4-acetylated fraction of SMX was the difference between the total and free fractions. TMP did not interfere with the SMX determination and vice versa. Except for N^4-acetyl SMX, these results were treated by nonlinear regression analysis for computation of pharmacokinetic parameters. The elimination of TMP and SMX from the plasma appeared to follow first-order kinetics.

The minimum inhibitory concentration (MIC) of TMP-SMX, singly and in combination, against isolated pathogens was determined by a serial-dilution agar method, using 1 part of TMP and 19 parts of SMX. The drugs were added to Mueller-Hinton (Difco) medium to which was added 5% lysed horse blood for hydrolyzing any thymidine present in the medium. Twofold dilutions were made of each drug and the combination, beginning with 128 μ of TMP per ml and 608 μg of SMX per ml when used singly and 32 μg of TMP plus 608 μg of SMX per ml when used in combination. The plates containing drug were streaked with inoculum from a 10^{-3} dilution of an overnight broth culture by using a calibrated loop that delivered approximately 10^2 organisms. After incubation at 37°C for 18 h, the MICs were determined as the lowest concentration of drug that inhibited 90% or more of the growth, as compared to the control plate containing no drug. The assays were performed in triplicate.

RESULTS

The mean plasma concentrations of TMP and free SMX on days 1 and 4 are shown in Fig. 1 and 2. On day 1, the TMP and SMX concentrations after completion of the 1-h infusion were 3.4 ± 0.3 and 46.3 ± 2.7 μg/ml, respectively, and the ratio was approximately 1:14. This ratio remained relatively constant during the study period. Over the next 7 h, both drugs were eliminated from the plasma at about the same rate. At 8 h, the plasma drug concentrations of TMP and SMX were 1.8 ± 0.2 and 23.8 ± 3.4 μg/ml, respectively. On day 4, plasma concentrations of TMP and free SMX were significantly higher than those on day 1 during the 8-hr period ($P < 0.01$). Also, the plasma concentrations of TMP (5.6 ± 0.6 μg/ml) and SMX (70.6 ± 7.3 μg/ml) just before the onset of infusion (hour 0) were significantly above the concentrations at 8 h after the initial infusion on day 1 ($P < 0.01$). The peak plasma concentrations were again achieved at 1 h: 8.8 ± 0.9 μg/ml for TMP and 105.6 ± 10.9 μg/ml for SMX. At 8 h, the concentrations of TMP and SMX were 5.8 ± 0.8 and 69.0 ± 7.6 μg/ml, respectively. Figure 2 also depicts the concentration of the N^4-acetylated form of SMX. Four hours after the first infusion,

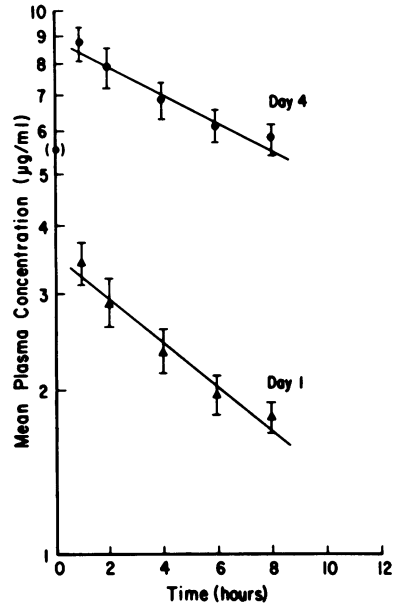

FIG. 1. *Mean plasma concentrations of TMP after the first dose and on day 4. Eleven patients were studied. The bars indicate the standard error of the mean.*

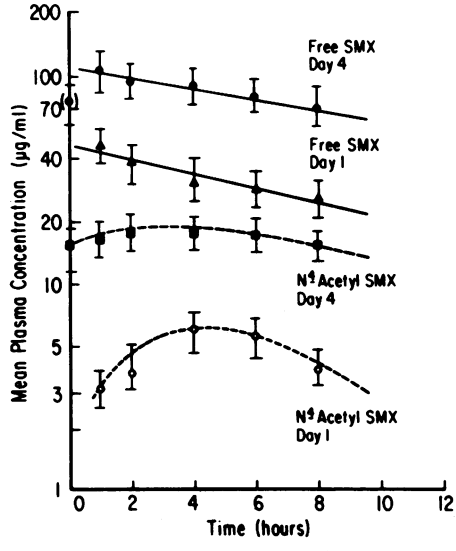

FIG. 2. *Mean plasma concentrations of free and N^4-acetylated SMX.*

and thereafter, the proportion of N^4-acetylated SMX remained at 14 to 17% of the total SMX concentration.

The plasma concentrations of TMP and SMX on day 1 were analyzed. The elimination of both agents from the plasma was found to be exponential as described by $C_t = 3.52 \exp(-0.0917t)$ and $C_s = 46.5 \exp(-0.0803t)$, in which C_t and C_s denote plasma concentrations (in micrograms per milliliter) of TMP and SMX, respectively, at time t (in hours). From these, mean plasma half-times of TMP and free SMX (± standard error) were estimated to be 7.7 ± 0.6 and 8.5 ± 1.4 h on day 1. On day 4, the plasma half-lives were 11.3 ± 0.7 and 12.8 ± 1.8 h, respectively. By extrapolation, the apparent volumes of distribution were 722 ± 64 ml/kg for TMP and 272 ± 29 ml/kg for SMX. The plasma clearance rates on day 1 were estimated to be 1.13 ± 0.12 ml/kg per min for TMP and 0.04 ± 0.03 ml/kg per min for SMX.

The amount of SMX and TMP recovered in the urine with time is listed in Table 1. With TMP, 21.6% of the dose was excreted in the urine over the 8-h collection period, 8.2% in the first 4 h and 13.4% in the last 4 h. About 22% of free SMX was excreted in the urine over the same time interval; 7.5% was recovered during the first 4 h, and 14.5% during the last 4 h. The ratio of TMP to free SMX in the urine was approximately 1:5 during both 4-h intervals. Over the 8-h collection period, the total SMX recovered was 253.7 mg, or 31.7% of the dose. Of this amount, 30% appeared in the urine as the acetylated form. Thus, approximately ⅔ of the total SMX excreted was the active unmetabolized drug.

Among the 11 patients in the study, 2 patients could not be evaluated for response to TMP-SMX therapy. One patient was subsequently found to have *Candida tropicalis* pneumonia and septicemia. A second patient had mixed *Klebsiella pneumoniae* and *Enterobacter cloacae* pneumonia and could not be evaluated because the organisms were not available for susceptibility testing. Six of the remaining nine patients were cured of their infection. Of the eight patients who were being treated for pneumonia, five responded to therapy; two of the four infections caused by *K. pneumoniae* and three of the four infections caused by unknown pathogens responded. The ninth patient, who was treated for *Staphylococcus aureus* sinusitis, responded to the therapy. Table 2 lists the infecting organisms and the corresponding MICs required to inhibit them in vitro.

All measurements of serum glutamic oxaloacetic transamonase, bilirubin, blood urea nitro-

TABLE 1. *Urinary excretion of SMX*

Time of urine collection (h)	TMP recovered			Free SMX recovered			N^4-acetylated SMX recovered		
	Concn (mg/dl)	Amt (mg)[a]	% of dose	Concn (mg/dl)	Amt (mg)[a]	% of dose	Concn (mg/dl)	Amt (mg)[a]	% of dose
0–4	38.4 ± 8.0	13.2 ± 2.6	8.2	137.6 ± 31.9	60.2 ± 14.7	7.5	41.1 ± 12.1	19.3 ± 7.4	2.1
4–8	45.6 ± 6.6	21.5 ± 7.0	13.4	237.0 ± 34.9	116.4 ± 36.1	14.5	146.7 ± 34.7	57.8 ± 16.6	6.2
0–8		34.7 ± 9.3	21.6		176.6 ± 39.1	22.1		77.2 ± 19.0	8.3

[a] Mean ± standard error of the mean.

TABLE 2. *MICs against organisms and outcome of infection*

Organism	MIC (μg/ml)			Outcome
	TMP	SMX	TMP + SMX	
S. aureus	2	38	0.25 + 4.75	Responded
K. pneumoniae	0.5	76	0.5 + 9.5	Responded
K. pneumoniae	64	304	8 + 152	Failed
K. pneumoniae	0.5	608	0.25 + 4.75	Responded
K. pneumoniae	16	304	8 + 152	Failed

gen, and creatinine, and all urinalyses, remained normal during and at the termination of therapy. No untoward reactions or symptoms attributable to TMP-SMX administration were observed.

DISCUSSION

The administration of 160 mg of TMP and 800 mg of SMX intravenously over a 1-h period resulted in a mean peak plasma concentration of TMP of 3.4 ± 0.3 μg/ml and a mean peak plasma concentration of SMX of 46.3 ± 2.7 μg/ml. The plasma concentration of TMP was maintained above 2 μg/ml for 4 h in 7 of the 11 patients studied. The plasma concentration of SMX was maintained above 20 μg/ml for 8 h in 9 of the 11 patients. Most infecting organisms are inhibited in vitro by disks containing 1.25 μg of TMP per ml and 23.75 μg of SMX per ml (5). The mean plasma concentrations of TMP were consistently nearly 2 times higher after intravenous administration than after oral administration (Table 3). However, the mean plasma concentrations of free SMX 4 and 8 h after drug administration were only 20 to 30% higher when given intravenously. During the first 2 h, the plasma concentrations were substantially higher after intravenous administration. The plasma half-life of SMX is similar following both routes of administration (12, 19). The plasma half-life of TMP after intravenous administration was 7.7 h in our study, which compares to the elimination half-life of 8.6 h observed by Schwartz and Rieder after oral administration (17). However, longer half-lives of 11.0 h to 14.5 h have been observed by other investigators following oral administration (12, 19). The longer half-life of TMP after oral administration may be due to prolonged absorption from the gastrointestinal tract or enterohepatic circulation of the drug. Four hours after drug administration, the concentration of TMP in bile is higher than in plasma (16).

The plasma concentrations of both TMP and SMX were significantly higher on day 4 than on day 1. This is not surprising because the schedule of drug administration was every 8 h, which was similar to the half-lives of the drugs. Substantial concentrations of both drugs were still detected in the plasma 8 h after the beginning of the first infusion. The ratio of TMP to free SMX remained relatively constant (day 1, 1:14, day 4, 1:12), suggesting no major alteration in the handling of these two drugs on prolonged administration. Kaplan et al. also found increasing plasma concentrations with repeated oral dosage (12). They used a 6-h interval between each of two doses with a 12-h interval between the third dose and the first dose of the next day. They concluded that it was possible to predict accurately the plasma concentrations, thus substantiating the constancy of the pharmacokinetics of these drugs. Lewin et al., however, observed no drug accumulation following multiple doses given by a twice-daily schedule (13).

TABLE 3. *Plasma concentrations after oral and intravenous administration of TMP-SMX*

Drug	Concn (μg/ml) at hour:				Plasma half-life (h)
	1	2	4	8	
TMP					
Oral[a]	1.7	1.6	1.4	1.0	8.6–14.5
Intravenous	3.4	2.9	2.3	1.8	7.6
Free SMX					
Oral[a]	13.2	22.3	26.1	18.1	9.0–11.0
Intravenous	46.3	38.7	30.6	23.8	8.6

[a] From ref. 2.

The optimum dosage schedule of TMP-SMX has not been determined. Insufficient numbers of patients were included in this study to accurately determine efficacy and toxicity; however, no side effects were observed, and six of the nine patients who could be evaluated were cured of their infection. The plasma concentration-MIC ratio required to produce optimum therapeutic results has not been determined but is probably at least 4. Since the serum half-lives of both drugs are long, they could be administered at less frequent intervals, or the dose could be reduced with repeated administration.

Renal excretion plays the largest role in the elimination of TMP and SMX from the body. SMX is metabolized to a varying degree in the body tissues, primarily in the liver, where

acetylation and oxidation occur. The major metabolite recovered in the blood and urine is the N^4-acetylated sulfonamide, which was the one measured in our study. About ⅔ of the excreted drug is unchanged. In contrast, little metabolism of TMP (primarily by conjugation in the liver) occurs in the body tissues, and the drug is excreted largely unchanged, with only approximately 7% of its conjugates recovered in the urine within 48 h (4).

Our pharmacokinetic data support the awareness that TMP has a greater propensity of tissue penetration than does SMX. This was borne out by the fact that the TMP-SMX ratio of 1:5 in the fixed drug combination was altered to be approximately 1:14 after administration. Also, TMP was determined to have a larger volume of distribution than SMX. Higher concentrations of TMP relative to those in the serum have been observed in the sputum (2, 11) and in the lung tissue (9) of patients receiving this drug. This may in part account for the fairly good responses seen in our patients treated for pneumonia.

In conclusion, our data indicate that good plasma and high urinary levels of TMP and SMX are achieved and maintained by administering the drug combination intravenously in our dosage schedule. This mode of administration was well tolerated by the patients, and no drug-related toxicity was observed. Also, it would be especially useful in patients who are unable to tolerate oral medications. It is anticipated that the intravenous preparation of TMP-SMX will play an important role in the future management of many infections.

ACKNOWLEDGMENTS

This work was supported in part by Public Health Service grant CA 05831 and contract NO1-CM-533773 from the National Cancer Institute and by a grant-in-aid from Hoffman-La Roche, Inc., Nutley, N.J.

LITERATURE CITED

1. **Bach, M. C., and M. Finland.** 1973. Susceptibility of recently isolated pathogenic bacteria to trimethoprim and sulfamethoxazole, separately and combined. J. Infect. Dis. **128**(Suppl.):508–533.
2. **Bach, M. C., O. Gold, and M. Finland.** 1973. Absorption and urinary excretion of trimethoprim, sulfamethoxazole, and trimethoprim-sulfamethoxazole: results with single doses in normal young adults and preliminary observations during therapy with trimethoprim-sulfamethoxazole. J. Infect. Dis. **128**(Suppl.):584–598.
3. **Bratton, A. C., and E. K. Marshall, Jr.** 1939. A new coupling component for sulfanilamide determination. J. Biol. Chem. **128**:537–550.
4. **Brumfitt, W., M. C. Faiers, R. E. Pursell, D. S. Reeves, and A. R. Turnbull.** 1969. Bacteriological, pharmacological, and clinical studies with trimethoprim-sulfonamide combinations with particular reference to the treatment of urinary infections. Postgrad. Med. J. **45**(Suppl.):32–37.
5. **Bushby, S. R. M.** 1973. Trimethoprim-sulfamethoxazole: in vitro microbiological aspects. J. Infect. Dis. **128**(Suppl.):442–462.
6. **Bushby, S. R. M., and G. S. Hitchings.** 1968. Trimethoprim, a sulfonamide potentiator. Br. J. Pharmacol. Chemother. **33**:73–90.
7. **Grose, W. E., G. P. Bodey, and V. Rodriguez.** 1977. Sulfamethoxazole-trimethoprim for infections in cancer patients. J. Am. Med. Assoc. **237**:352–354.
8. **Grunbert, E., and W. F. DeLorenzo.** 1966. Potentiation of sulfonamides and antibiotics by trimethoprim (2,4-diamino-5-trimethoxybenzyl) pyrimidine, p. 430–433. Antimicrob. Agents Chemother. 1966.
9. **Hansen, I., L. Neilsen, and S. Bertelsen.** 1973. Trimethoprim in human saliva, bronchial secretion and lung tissue. Acta Pharmacol. Toxicol. **32**:337–344.
10. **Hitchings, G. .** 1969. Species differences among dihydrofolate reductases as a basis for chemotherapy. Postgrad. Med. J. **45**(Suppl.):7–10.
11. **Hughes, D. T. D.** 1969. Single-blind comparative trial of trimethoprim-sulfamethoxazole and ampicillin in treatment of exacerbations of chronic bronchitis. Br. Med. J. **4**:470–473.
12. **Kaplan, S. A., R. E. Weinfeld, C. W. Abruzzo, K. McFadden, L. M. Jack, and L. Weissman.** 1973. Pharmacokinetic profile of trimethoprim-sulfamethoxazole in man. J. Infect. Dis. **128**(Suppl.):547–555.
13. **Lewin, E. B., J. O. Klein, and M. Finland.** 1973. Trimethoprim-sulfamethoxazole: absorption, excretion and toxicity in six children. J. Infect. Dis. **128**(Suppl.):618–621.
14. **Marks, M. I.** 1975. Pharmacokinetics and efficacy of trimethoprim-sulfamethoxazole in the treatment of gastroenteritis in children. Can. Med. Assoc. J. **112** (Suppl.):33–34.
15. **Rieder, J.** 1973. Excretion of sulfamethoxazole and trimethoprim into human bile. J. Infect. Dis. **128**(Suppl.): 574.
16. **Schwartz, D. E., B. A. Koechlin, and R. E. Weinfeld.** 1969. Spectrofluorometric methods for the determination of trimethoprim in body fluids. Chemotherapy **14**(Suppl.):22–29.
17. **Schwartz, D. E., and J. Rieder.** 1970. Pharmacokinetics of sulfamethoxazole and trimethoprim in man and their distribution in the rat. Chemotherapy **15**:337–355.
18. **Wellcome Foundation Symposium.** 1975. Combination chemotherapy of infectious disease. Can. Med. Assoc. J. **112**(Suppl.):1–100.
19. **Welling, P. G., W. A. Craig, G. L. Amidon, and C. M. Kunin.** 1973. Pharmacokinetics of trimethoprim and sulfamethoxazole in normal subjects and in patients with renal failure. J. Infect. Dis. **128**(Suppl.):556–566.
20. **Wilfert, C. M.** 1973. Trimethoprim-sulfamethoxazole in children: pharmacokinetics and clinical studies. J. Infect. Dis. **128**(Suppl.):613–617.