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Pharmacokinetics of Trimethoprim and Sulfamethoxazole in Serum and Cerebrospinal Fluid of Adult Patients with Normal Meninges

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The pharmacokinetics of trimethoprim (TMP) and sulfamethoxazole (SMX) in cerebrospinal fluid (CSF) and serum after a single intravenous infusion of 5 mg of TMP and 25 mg of SMX per kg of body weight over approximately 120 min were studied in nine patients who had uninflamed meninges and were undergoing elective myelography. Peak concentrations of TMP and SMX in CSF were 1 μg/ml and 13.8 μg/ml, respectively. The peak TMP concentration in CSF occurred significantly earlier than the peak SMX concentration (60 versus 480 min postinfusion). At 15 h, there was no detectable TMP in the CSF, and there was 4.7 μg of SMX per ml of CSF. In the postdistribution phase (in CSF), simultaneous CSF-to-serum concentration ratios ranged from 0.23 to 0.53 for TMP and from 0.20 to 0.36 for SMX. CSF penetration (measured by comparison of the area under the curve of the composite CSF and serum concentration-time curves) was 18% for TMP and 12% for SMX. A loading dose of TMP-SMX (based on TMP) of 10 to 12 mg/kg and a maintenance dose of 6 mg/kg every 8 h or 8 mg/kg every 12 h (with a 2-h infusion) should yield steady-state peak concentrations of at least 5 μg of TMP per ml of serum and 160 μg of SMX per ml of serum. Further studies of TMP-SMX administered in these doses in the treatment of serious bacterial infections, including meningitis, are warranted.

The recent availability of an intravenous formulation of trimethoprim-sulfamethoxazole (TMP-SMX) has facilitated the use of higher doses of this combination in the treatment of serious bacterial infections, including meningitis (3, 5, 15, 20–22, 28, 29). Unfortunately, detailed information on the serum pharmacokinetics and tissue penetration of TMP-SMX after a single large intravenous dose is lacking. In view of the usefulness of this combination in the treatment of human infections, including meningitis, we studied the pharmacokinetics of TMP-SMX in the serum and cerebrospinal fluid (CSF) of adult patients undergoing elective myelography.

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MATERIALS AND METHODS

Patients. Nine patients (six women and three men) who were thought to have vertebral disk disease and had been admitted to Hartford Hospital for elective myelography were studied. The average (range) age, height, and total body weight were 44 years (19 to 74 years), 165 cm (158 to 185 cm), and 65 kg (54 to 77 kg), respectively. Informed consent was obtained from each patient according to the guidelines of our institution. All of the patients had a negative history for underlying renal and hepatic disease and for allergy to TMP and sulfa-type drugs and were normal for the following laboratory tests: complete blood count, serum creatinine level, and blood urea nitrogen level. CSF samples taken from all patients showed no evidence of meningeal inflammation.

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Dosing and sample collection. An intravenous preparation of TMP-SMX was supplied as 5-ml ampoules, each of which contained 80 mg of TMP (16 mg/ml) and 400 mg of SMX (80 mg/ml) (Bactrim, Hoffmann–LaRoche Inc., Nutley, N.J.). Each patient received a single 5-mg dose of TMP plus a 25-mg dose of SMX per kg (based on total body weight) prepared in 400 ml of 5% glucose in water. The total dose was infused intravenously over approximately 120 min within 3 h of preparation.

Single CSF samples were obtained by lumbar puncture 142 to 900 min after the start of drug infusion and before the introduction of radio-opaque dye. Blood samples were collected from a peripheral intravenous catheter for the first 12 h of study and then by direct venipuncture. At least three serum samples were obtained from each patient, usually during and at the conclusion of drug infusion, and always at the time of CSF collection. In the six patients who participated in the serum pharmacokinetic study, a total of 6 to 10 blood samples were obtained from each patient up to 48 h after the start of the drug infusion. Serum and CSF samples were stored at −80°C until assay.

TABLE 1. Concentrations of TMP and SMX in CSF and serum in nine patients

Time after start of infusion (min)	Concn (μg/ml) in CSF/concn in serum (CSF/serum ratio)	
	TMP	SMX
142	0.8/3.5 (0.23)	10.3/87.2 (0.12)
160	1.0/1.9 (0.53)	2.5/75.1 (0.03)
200	0.9/2.9 (0.31)	3.1/66.0 (0.05)
258	0.8/1.5 (0.53)	5.7/59.4 (0.10)
295	0.7/1.8 (0.39)	6.3/75.3 (0.08)
332	0.7/1.6 (0.44)	13.0/55.9 (0.23)
365	0.5/1.6 (0.31)	13.8/38.0 (0.36)
517	0.3/1.1 (0.27)	10.3/48.1 (0.21)
900	ND[a]/1.0	4.7/23.1 (0.20)

[a] ND, Not detectable.

TABLE 2. Pharmacokinetics of TMP and SMX in CSF[a]

Drug	AUC (mg h liter^{-1})	$t_{1/2}$ of terminal slope (h)	Peak CSF peak serum ratio	CSF penetration[b]
TMP	5.4	3.4	0.34	0.18
SMX	141	5.7	0.17	0.12

[a] Obtained by composite analysis of drug concentrations in single CSF samples obtained from nine patients at different times.
[b] AUC for CSF/AUC for serum.

Assay. Serum and CSF samples were assayed by high-pressure liquid chromatography with a Vista 402 data system and series 5000 L.C. (Varian Associates, Walnut Creek, Calif.). Standard concentrations of TMP (0.1 to 12 μg/ml) and SMX (1 to 100 μg/ml) were prepared in pooled sera (serum samples) or buffer (CSF samples). Paranitrophenol (5 μg/ml) was used as an internal standard. Protein was precipitated by combining 0.5 ml of sample (or drug standard) with 0.25 ml of internal standard and 1 ml of acetonitrile. This mixture was vortexed for 30 s and then centrifuged at 3,250 × *g* for 15 min. A 50-μl sample of the resulting supernatant was injected into the instrument.

Analytical conditions consisted of a phase of 25% acetonitrile and 75% 0.02 M Sorenson buffer (pH 3.0). The mobile phase was passed through a C-18, 5-μm column (column head pressure = 1,500 lb/in^2) at a flow rate of 1.5 ml/min. The UV absorption was adjusted for 235 nm at 0.04 absorbance units, full scale. Column retention times for TMP, SMX, and internal standard were 6.6, 9.4, and 13.1 min, respectively.

Serum standards were prepared in pooled serum at concentrations of 0.5, 1, 3, 5, 7, and 10 μg of TMP per ml and 5, 20, 40, 60, 80, and 100 μg of SMX per ml. Precision, accuracy, and linearity of detector response were determined based on triplicate determinations of each standard on three separate runs (inter- and intrarun). The precision of the TMP assay for all standards ranged from 0.8 to 1.5%; for the SMX assay, precision ranged from 1.2 to 8.5%. Accuracy ([|measured-actual/actual|] × 100%) ranged from 0 to 4% for TMP and 0 to 18% for SMX. The linearity of detector response for TMP was as follows: slope, 8.50; *y* intercept, 0.010; correlation coefficient, 0.9999. For SMX, the values were: slope, 0.330; *y* intercept, 0.340; correlation coefficient, 0.9997. The lower limit of sensitivity in serum was 0.1 μg/ml for TMP and 5 μg/ml for SMX; for aqueous samples, the sensitivity was 0.1 and 1 μg/ml for TMP and SMX, respectively.

Pharmacokinetic analysis. Noncompartmental methods were used for determination of pharmacokinetic parameters (9). The area under the curve (AUC) from time = 0 to ∞ of the composite cerebrospinal fluid concentration-time and serum concentration-time curves were calculated with the linear trapezoidal rule. The terminal disposition rate constant (λ_z) was calculated by least-squares linear regression of the terminal linear portion of the serum or composite CSF-versus-time curve. Elimination half-life ($t_{1/2}$), total serum clearance (CL), and the volume of distribution at steady state (V_{ss}) and during the elimination phase (V_{area}) were calculated by standard equations (9).

RESULTS

Concentrations of TMP and SMX in CSF are shown in Table 1, and the pharmacokinetics are summarized in Table 2. The highest concentration of TMP in CSF (1 μg/ml) was measured in the sample collected 160 min after the start of the infusion. In contrast, the appearance of SMX in CSF was generally delayed; the peak SMX concentration in CSF (13.8 μg/ml) appeared approximately 6 h after the start of drug infusion. The ratio of detectable TMP to SMX concentrations in CSF ranged from 1:3 to 1:34. The $t_{1/2}$s of TMP and SMX in CSF were 3.4 and 5.7 h, respectively.

Concentrations of TMP and SMX in serum are shown in Table 3. The decline in these concentrations demonstrated variable distribution patterns. There was a distinct distribution phase in the TMP and SMX serum concentration-time curve characteristic of a two-compartment body model in only three patients for each drug (patients 1, 2, and 4 for TMP and patients 2, 3, and 6 for SMX). Mean (± standard deviation) peak concentrations of TMP and SMX in serum were 2.9 (±0.9) μg/ml and 82.9 (±9.5) μg/ml, respectively. Table 4 summarizes the serum pharmacokinetics of TMP

TABLE 3. Concentrations of TMP and SMX in serum

Patient	Concn (μg/ml) of TMP/concn of SMX[a] in serum sample no.:									
	1	2	3	4	5	6	7	8	9	10
1	0.8/40.3 (30)	3.3/80.0 (155)	2.9/66.0 (220)	1.4/65.0 (336)	0.9/21.0 (641)	0.3/18.8 (1,250)				
2	1.9/43.3 (30)	2.9/99.3 (112)	2.3/59.0 (148)	1.5/66.4 (180)	1.0/48.1 (300)	0.9/48.1 (499)	0.8/40.4 (643)	0.4/17.2 (1,444)		
3	2.6/93.1 (76)	2.4/72.6 (103)	1.9/71.4 (133)	1.8/62.3 (248)	1.6/55.9 (346)	1.4/49.0 (413)	1.3/40.4 (580)			
4	0.8/34.0 (28)	4.6/82.2 (132)	3.5/74.0 (162)	1.4/72.0 (200)	1.5/59.4 (278)	1.1/52.0 (418)	0.9/53.0 (673)	0.3/19.2 (1,370)	0.1/10.8 (1,645)	ND[b]/6.9 (1,795)
5	0.6/31.6 (32)	2.8/86.0 (135)	2.6/71.3 (165)	1.8/75.3 (315)	1.2/57.1 (480)	1.1/34.3 (669)	0.4/20.3 (1,415)	0.1/9.3 (2,020)	ND/<5 (2,880)	
6	0.8/39.1 (30)	3.5/87.2 (132)	3.3/75.4 (172)	3.1/68.7 (205)	2.8/59.1 (300)	2.1/53.2 (472)	0.6/22.4 (1,200)	0.2/16.4 (1,437)		
7	2.3/81.4 (105)	1.3/40.8 (595)	1.1/33.3 (720)	1.0/23.1 (920)						
8	1.2/37.0 (30)	1.9/75.1 (180)	1.8/61.8 (310)							
9	1.9/53.0 (40)	2.3/69.7 (180)	1.6/38.0 (370)							

[a] Values in parenthesis refer to time of sampling (min) after the start of infusion.
[b] ND, Not detectable.

TABLE 4. Serum pharmacokinetic parameters of TMP and SMX

Patient	AUC (mg h liter^{-1})[a]	λ_z (h^{-1})	$t_{1/2}$ (h)	CL (ml min^{-1})	CL (ml min kg^{-1})	V_{ss} (liters)	V_{ss} (liters kg^{-1})	V_{area} (liters)	V_{ss} (liters kg^{-1})
1	26.7/1,010	0.102/0.072	6.8/9.6	216/28.4	3.1/0.41	106/22.6	1.5/0.33	127/23.7	1.8/0.34
2	28.1/1,250	0.058/0.055	11.9/12.6	181/20.9	3.0/0.33	159/20.2	2.6/0.33	187/22.4	3.1/0.39
3	30.4/1,040	0.080/0.072	8.7/9.6	148/21.7	2.7/0.40	122/18.7	2.3/0.35	111/18.0	2.1/0.33
4	27.6/1,220	0.093/0.078	7.4/8.9	219/23.2	3.2/0.34	121/17.0	1.8/0.25	133/17.8	2.0/0.26
5	31.5/1,190	0.096/0.084	7.2/8.2	207/25.6	2.8/0.35	120/17.0	1.6/0.27	121/18.3	2.6/0.25
6	41.6/1,230	0.102/0.070	6.8/10.0	156/24.7	2.1/0.34	81/19.7	1.1/0.27	86/21.1	1.2/0.29
Mean ± SD	32.6/1,160 ± 6.6/103	0.089/0.072 ± 0.02/0.010	8.1/9.8 ± 2.0/1.5	188/24.1 ± 30.8/2.7	2.8/0.36 ± 0.4/0.03	118/19.6 ± 25.4/1.9	1.8/0.30 ± 0.5/0.04	127/20.2 ± 33.6/2.5	2.0/0.31 ± 0.06/0.05

[a] Parameter for TMP/parameter for SMX.

and SMX in six patients. The mean serum $t_{1/2}$s of TMP and SMX were 8.1 h and 9.8 h, respectively. The V_{ss} and CL of TMP were significantly larger than those observed for SMX.

No untoward reactions attributable to TMP-SMX administration were observed.

DISCUSSION

Previous studies on the pharmacokinetics of TMP-SMX in CSF have been primarily limited to children (1, 2, 12, 13, 19, 26,). Only a few studies have reported concentrations of TMP and SMX in the CSF of adults after intravenous doses (10, 14, 25). Moreover, variable results have been observed because of differences in patient population studied, dose, timing of sample collection, duration of therapy, assay methodology, and reliance on CSF-to-serum concentration ratios to describe CSF penetration. Our study demonstrates that diffusion of SMX into CSF is slow, as peak concentrations occur approximately 6 h after the start of drug infusion; these findings are consistent with those of a previous study of a single 2-g oral dose in adults (4). The prolonged distribution of SMX into CSF indicates that CSF-to-serum concentration ratios may be an unreliable measure of CSF penetration, as early paired CSF and serum samples would tend to yield low CSF-to-serum ratios. Comparison of the relative availability of both drugs to CSF (obtained by comparison of the AUC in serum and CSF) indicates that despite the delayed distribution of SMX into CSF, both drugs have similar CSF penetration.

The ratio of TMP to SMX concentrations in CSF was often within the range of 1:5 to 1:40 that appears to be optimum for synergy in vitro. Although the in vivo significance of synergy between these compounds is controversial, it may be of greatest clinical significance at relatively low concentrations of these agents (6).

Higher concentrations of TMP and SMX in CSF have been measured in adult and pediatric patients with and without meningitis after multiple oral or intravenous doses (1, 2, 8, 10, 12–14, 19, 25, 26). These data suggest that accumulation of TMP and SMX occurs in CSF as in serum with an 8- or 12-h dosage interval and is consistent with our data after a single dose. Previous studies in humans and animals also suggest little correlation between meningeal inflammation and concentrations of TMP and SMX in CSF (1, 2, 8, 10, 12–14, 17–19, 25, 26). The excellent penetration of TMP and SMX into CSF through uninflamed meninges provides a pharmacokinetic rationale for the use of this combination in the prophylaxis or treatment of central nervous system infections in which meningeal inflammation is low or absent (e.g., CSF shunts) (27).

Stability problems with the intravenous formulation of TMP-SMX necessitates the use of large fluid volumes for administration and longer infusion times. Despite the use of a 2-h infusion, peak TMP and SMX concentrations were high and consistent with previous simulations, demonstrating a lack of significant effect of prolonged infusions on the postdistribution peak concentrations of TMP and SMX (16). The CL, V_{ss}, and $t_{1/2}$ of TMP-SMX calculated in our patients are compatible with those reported by others using smaller intravenous doses; however, these studies provided only rough estimates of these parameters because of multiple-dose design or short serum sampling periods (7, 11, 16, 23, 24). By using the pharmacokinetic parameters generated from our data, a loading dose of 10 to 12 mg of TMP per kg (50 to 60 mg of SMX per kg) over the first 8 h and a maintenance dose of 5 to 6 mg of TMP per kg (25 to 30 mg of SMX per kg) infused over 2 h every 8 h would provide 1-h postinfusion peak concentrations of at least 5 μg of TMP per ml and 160 μg of SMX per ml at steady state; these concentrations may be obtained alternatively with a dose of 8 mg of TMP per kg (40 mg of SMX per kg) every 12 h (9). These dosage recommendations are slightly higher than those recommended by Siber et al. (23), but they are consistent with the differences in infusion time, estimation of pharmacokinetic parameters, and use of 1-h postinfusion (postdistribution) peak in our calculations. Our dosage recommendations are also more consistent with the doses used in reports of successful therapy of serious infections (3, 5, 20–22, 28).

The clinical role of TMP-SMX in the treatment of serious infections continues to evolve. Further study of higher doses of this combination in the treatment of serious infections, including meningitis, due to certain pathogens (e.g., *Acinetobacter* sp., *Serratia* sp., *Listeria* sp., and *Enterobacter* sp.) are warranted.

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