Pharmacokinetics and Adverse Effects of 20-mg/kg/Day Trimethoprim and 100-mg/kg/Day Sulfamethoxazole in Healthy Adult Subjects

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The pharmacokinetics of trimethoprim-sulfamethoxazole were studied in 12 healthy adult subjects receiving trimethoprim at 20 mg/kg of body weight per day and sulfamethoxazole at 100 mg/kg/day, which is the conventional dose for treating Pneumocystis carinii pneumonia (PCP). Daily doses were evenly divided and orally administered every 6 h for 3 days. Trimethoprim, sulfamethoxazole, and N4-acetylsulfamethoxazole concentrations in serum and urine were measured by high-performance liquid chromatography. Five subjects withdrew from the study because of intolerable gastrointestinal and central nervous system toxicities. In the seven subjects that completed the study, the mean maximum serum drug concentrations after the last dose were 13.6 ± 2.0, 372 ± 64, and 50.1 ± 10.9 μg/ml for trimethoprim, sulfamethoxazole, and N4-acetylsulfamethoxazole, respectively. The mean half-lives were 13.6 ± 3.5, 14.0 ± 2.3, and 18.6 ± 4.3 h, respectively. Changes in absolute neutrophil count were significantly correlated with the minimum concentrations of trimethoprim and sulfamethoxazole in serum and trimethoprim area under the concentration-time curve (for all three parameters, r² = 0.6 and P < 0.05). Our findings add to the evidence that serum drug concentrations in adults following the conventional dose of trimethoprim-sulfamethoxazole for PCP are excessive and contribute to severe adverse reactions. Further studies are indicated in patients to optimize the dosing regimen of trimethoprim-sulfamethoxazole in the treatment of PCP.

Pneumocystis carinii pneumonia (PCP) is the most prevalent opportunistic infection in patients infected with human immunodeficiency virus type 1 (HIV), with over 80,000 cases reported since 1981 (3). This pneumonia accounts for 60% of the index diagnoses of AIDS, and approximately 80% of patients will develop an episode of PCP during their course of HIV infection (2). About 90% of patients with mild to moderate disease will respond with early initiation of therapy; however, in nearly 25% of patients, this pneumonia has been a major cause of mortality (13). Although widespread use of anti-Pneumocystis pneumonia chemoprophylaxis will potentially reduce the incidence of PCP in HIV-infected patients, efforts focused on optimizing the acute management of this life-threatening infection nonetheless are warranted.

Trimethoprim-sulfamethoxazole in a daily dose of 20 and 100 mg/kg of body weight, respectively, is a standard therapeutic modality for the treatment of PCP in AIDS patients, despite a greater than 60% incidence of adverse reactions during treatment (1, 9, 12, 17, 23). Many of these reactions are severe and result in discontinuation of trimethoprim-sulfamethoxazole therapy. The etiology of this observed high incidence of toxicity is not fully elucidated. Recent reports, however, indicate that several of these adverse reactions may be pharmacodynamic manifestations of the drug secondary to concentration-dependent toxicities. Trimethoprim and sulfamethoxazole each have been demonstrated in vitro to inhibit hematopoiesis in a dose-dependent manner (8). Sattler et al. (19) demonstrated that adjusting the trimethoprim-sulfamethoxazole dose to maintain serum trimethoprim concentrations at 5 to 8 μg/ml decreased toxicity without an apparent diminution in efficacy. In addition, preliminary data indicate that maintaining the peak serum sulfamethoxazole concentration below 200 μg/ml may decrease the incidence of leukopenia (5).

The current dosing recommendation of 20-mg/kg/day trimethoprim and 100-mg/kg/day sulfamethoxazole for treatment of PCP originated from studies in pediatric cancer patients. This represents an atypical establishment of an adult therapeutic dosage regimen, since the milligram-per-kilogram dose was directly extrapolated from the pediatric population. It is well documented that the relationship between comparable dose and the achieved serum drug concentration can be significantly different between adult and pediatric patients (18). This relationship needs to be evaluated as a mechanism contributing to the high rate of drug toxicity observed in adult AIDS patients. Excessive drug concentrations due to differences in the pharmacokinetic disposition of trimethoprim and sulfamethoxazole in adults compared with that in children could result in an increased incidence of concentration-dependent toxicities in the former group. The objective of this study was to determine the pharmacokinetic profile of trimethoprim-sulfamethoxazole following daily dosing of 20 and 100 mg/kg, respectively, in healthy adult subjects.

(Materials and Methods)

Subjects. Twelve healthy nonsmoking male volunteers gave written informed consent prior to participation in this study, which was approved by the Institutional Review Board. Twelve healthy adult men were randomized to receive trimethoprim-sulfamethoxazole at a dosage of 20 mg/kg of body weight/day of trimethoprim and 100 mg/kg/day of sulfamethoxazole for 3 days. Doses were evenly divided and given orally every 6 h.

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Subjects. Twelve healthy nonsmoking male volunteers gave written informed consent prior to participation in this study, which was approved by the Institutional Review Board. Twelve healthy adult men were randomized to receive trimethoprim-sulfamethoxazole at a dosage of 20 mg/kg of body weight/day of trimethoprim and 100 mg/kg/day of sulfamethoxazole for 3 days. Doses were evenly divided and given orally every 6 h.
Board of the University of Tennessee, Memphis. Each subject was in good health before study participation as indicated by medical history, physical examination, and laboratory measurements (hematology, blood chemistry profiles, urinalysis, 24-h creatinine clearance) assessed within 1 week of study initiation. No subject had a history of renal, hepatic, gastrointestinal, cardiovascular, or hematologic disease. No subject had a known previous hypersensitivity reaction to trimethoprim, sulfamethoxazole, or one of their derivatives. All subjects refrained from alcohol ingestion throughout the study period, and none of the subjects were receiving concurrent medication. Poststudy laboratory tests were performed 72 h after administration of the last scheduled dose.

**Drug administration.** Subjects ingested 5 mg of trimethoprim and 25 mg of sulfamethoxazole per kilogram of body weight orally every 6 h for 13 consecutive doses (equivalent to 3 days of conventional pneumocystis pneumonia dosing of 20-mg/kg/day trimethoprim and 100-mg/kg/day sulfamethoxazole). The dosing regimen was designed to assure attainment of steady-state serum drug concentrations before serial collection of blood samples for pharmacokinetic analysis. Single-strength trimethoprim-sulfamethoxazole tablets (80 mg of trimethoprim and 400 mg of sulfamethoxazole; lot 9M2583 [Burroughs Wellcome Co., Research Triangle Park, N.C.]) were used for all doses. The amount of drug administered per dose was rounded to the nearest one-half single-strength tablet necessitated by the fixed amount of drug in tablet formulation. Subjects were instructed to fast for 1 h before and 2 h after each dose. A light snack (e.g., soda crackers) was allowed for subjective nausea. Compliance was assessed by tablet counts and documentation of administration times in the medication time log sheets maintained by each subject. Following an overnight fast, the last dose of trimethoprim-sulfamethoxazole was administered on the morning of the fourth day. Subjects continued to fast for 4 h postdose before being allowed to eat a standard lunch and dinner at 12 noon and 5 p.m., respectively. Prior to administration of the last dose, an indwelling venous catheter was inserted in an antecubital vein to facilitate blood sample collection.

**Sample collection.** Seven-milliliter blood samples were collected in plain red-top evacuated blood collection tubes prior to the first dose in the morning on study days 1, 2, and 3 by direct venipuncture. Additional blood samples (7 ml each) were obtained immediately before (0 h) and 10, 20, and 40 min and 1, 1.3, 1.7, 2, 2.3, 2.7, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, 48, and 72 h after the last dose. Samples were collected via the indwelling catheter for the first 12 h, while the remaining samples were obtained by direct venipuncture. After each blood sample was collected from the indwelling catheter, a 2-ml aliquot of saline flush was injected into the catheter to maintain patency. All samples were allowed to clot at room temperature for 30 min prior to centrifugation at 1,000 x g for 15 min. Urine samples were collected from each subject for one dosing interval (0 to 6 h) after the last dose. During the 6-h collection period, urine samples were stored in plastic containers at 4°C. The total volume of urine from a patient was measured at the end of the collection interval, and a 10-ml aliquot was retained. The decanted serum samples and urine aliquots were stored at −70°C until the time of assay.

**Analytical procedures.** The concentrations of trimethoprim, sulfamethoxazole, and N4-acetylsulfamethoxazole in serum and urine were determined by using an ion-paired high-performance liquid chromatography assay with the solid-phase extraction method previously developed in our laboratory (14). For all compounds assayed, the accuracy was −3.0 to 9.8%, and the coefficients of variation for within-day and between-day variation were 3.6 to 6.0 and 3.4 to 8.9%, respectively.

**Pharmacokinetic analysis.** Steady-state serum drug concentration-time data for trimethoprim, sulfamethoxazole, and N4-acetylsulfamethoxazole were analyzed by standard noncompartmental methods (7). The elimination rate constant (k) was estimated using a weighted (1/C2, where C is drug concentration) nonlinear least-squares regression analysis of the terminal phase of the concentration-time plot (PCNONLIN; Statistical Consultants Inc., Lexington, Ky.). The half-life was calculated by using 0.693/k. Area under the concentration-time curve during the steady-state dosing interval from 0 to 6 h (AUC) was calculated by the linear trapezoidal method. Total apparent oral clearance (CL/F) was estimated by the equation CL/F = dose/AUC. Renal clearance (CLR) was calculated from the relationship CLR = Ae/AUC, where Ae is the amount of unchanged drug excreted in the urine at steady state from 0 to 6 h. The apparent volume of distribution was calculated by the ratio of oral clearance to elimination rate constant. The maximum (Cmax) and minimum (Cmin) concentration of drug in serum and the time to achieve the maximum concentration were obtained directly from the concentration-time plots. The fraction of drug excreted unchanged in the urine (0 to 6 h) was calculated for all three compounds.

**Statistical analysis.** The relationships between changes in hematologic and blood chemistry laboratory indices versus various pharmacokinetic parameters were assessed by linear least-squares regression analyses with statistical significance determined by the F test. The Cmin values of trimethoprim and sulfamethoxazole were evaluated between subjects and days by analysis of variance for repeated measures with the Tukey’s test for multiple comparisons. A P value of <0.05 was considered significant.

**RESULTS**

**Pharmacokinetics.** The 12 subjects had a mean age of 28.2 ± 3.6 years (range, 22 to 32 years) and mean weight of 75.8 ± 8.6 kg (range, 61.1 to 89.1 kg). The mean dose for trimethoprim was 20.2 ± 0.6 mg/kg/day (range, 19.3 to 20.9 mg/kg/day), and the mean dose for sulfamethoxazole was 101.1 ± 3.1 mg/kg/day (range, 96.3 to 104.7 mg/kg/day).

Pharmacokinetic analyses were done for the data from the seven subjects that completed the study. Figure 1 shows the mean steady-state serum drug concentration-time curves for trimethoprim, sulfamethoxazole, and N4-acetylsulfamethoxazole. The mean values (ranges given in parentheses) of Cmax steady-state serum drug concentrations were 13.6 (10.6 to 16.1), 372 (277 to 469), and 50.1 (39.5 to 70.3) μg/ml for trimethoprim, sulfamethoxazole, and N4-acetylsulfamethoxazole, respectively. The mean values (ranges given in parentheses) of the time to achieve the maximum concentration for the three compounds were 1.9 (0.3 to 2.7), 2.6 (0.7 to 3.5), and 2.8 (0.3 to 6.0) h, respectively. Table 1 lists the means and standard deviations for the above values, along with the AUC, half-life, apparent volume of distribution, total apparent oral clearance, renal clearance, and urinary excretion data for the three compounds.

The Cmin values determined at the end of the 6-h dosing interval after the last dose administered on days 1, 2, and 3 are depicted in Fig. 2. No significant differences were detected between Cmin values for the five subjects that

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FIG. 1. Serum drug concentrations following the last dose for trimethoprim (TMP), sulfamethoxazole (SMX) and N-acetyl sulfamethoxazole (NSMX). The means ± standard deviations for seven subjects are shown.

FIG. 2. Minimum serum drug concentrations ($C_{\text{min}}$) of trimethoprim (TMP) and sulfamethoxazole (SMX) at the end of the 6-h dosing interval on days 1, 2, and 3 in healthy subjects. The values on day 3 are the $C_{\text{min}}$ following the last dose. Each symbol represents the $C_{\text{min}}$ in an individual subject on day 1 ($n=11$), day 2 ($n=8$), and day 3 ($n=7$). Bars indicate mean $C_{\text{min}}$ values. Asterisks indicate that the mean values are significantly different compared with day 1 values ($P < 0.05$).

withdraw from the study compared with the $C_{\text{min}}$ values for six of the seven subjects (one subject had inadequate blood sample collection) that completed the study at 24 h (mean trimethoprim $C_{\text{min}}$, 8.7 ± 1.2 versus 8.1 ± 2.3 µg/ml, respectively [$P = 0.61$]; mean sulfamethoxazole $C_{\text{min}}$, 220 ± 19 versus 205 ± 47 µg/ml, respectively [$P = 0.50$]). By the end of the first day of dosing, subjects did not achieve steady-state conditions. Mean trimethoprim and sulfamethoxazole $C_{\text{min}}$ values following the fourth dose on day 1 were 8.4 ± 1.9 and 212 ± 36 µg/ml, respectively ($n=11$). Drug accumulation continued through day 2 of dosing and did not change significantly thereafter. The mean $C_{\text{min}}$ values ($n=8$)
at the end of day 2 were 11.5 ± 1.8 μg/ml (P = 0.001 compared with day 1 C_{min}) for trimethoprim and 286 ± 45 μg/ml (P < 0.001 compared with day 1 C_{min}) for sulfamethoxazole. The end of day 3, mean C_{min} values (n = 7) of trimethoprim and sulfamethoxazole, respectively, were 10.6 ± 2.1 (P = 0.012) and 334 ± 62 (P < 0.001) μg/ml compared with day 1 values.

Toxicity. This dosing regimen of trimethoprim-sulfamethoxazole was not well tolerated by the 12 subjects. The documented adverse reactions are listed in Table 2. All subjects experienced some type of clinically significant gastrointestinal and central nervous system (CNS) toxicities. Five subjects were unable to complete the study because of intolerable adverse effects (nausea, headache, tremor, and jittery feeling). Four subjects, all of whom withdrew from the study, had several episodes of vomiting. Two subjects complained of being disoriented, which they described as not being acutely aware of their surroundings, including other people around them. These same two subjects also experienced a subjective decreased hearing sensitivity. One subject complained of a nonpruritic prickly sensation in his skin. No rash developed in any of the 12 participants. One subject developed diarrhea. All of these toxicities were of transient duration and resolved within 24 h after drug discontinuation.

In the seven subjects that pharmacokinetic parameters were determined, regression analyses established significant inverse relationships between absolute neutrophil count (ANC) and trimethoprim C_{min} (r^2 = 0.58, P = 0.047), sulfamethoxazole C_{min} (r^2 = 0.57, P = 0.049), and trimethoprim AUC (r^2 = 0.60, P = 0.041). Nonsignificant trends were found between ANC and sulfamethoxazole AUC (P = 0.063), ANC and trimethoprim C_{max} (P = 0.061), and ANC and sulfamethoxazole C_{max} (P = 0.109). The values for C_{max} and C_{min} in the above regressions are data obtained during the first 6 h following administration of the last dose. Comparison between pre- and poststudy laboratory values in all 12 subjects showed that 6 subjects had a decrease in blood glucose below 60 mg/dl (mean decrease, 40% ± 7%; range, 34 to 49%). The two subjects that complained of being disoriented were not hypoglycemic, defined as a blood glucose level of ≤60 mg/dl. Four subjects had a 1.5- to 2.0-fold increase in aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase. The leucocyte

### Table 1. Steady-state pharmacokinetic parameters for the seven subjects that completed the study

<table>
<thead>
<tr>
<th>Drug</th>
<th>C_{max} (μg/ml)</th>
<th>T_{max} (h)</th>
<th>AUC (mg·h/liter)</th>
<th>V/F (liter/kg)</th>
<th>CL/F (ml/min/kg)</th>
<th>CL_{ur} (ml/min/kg)</th>
<th>Urinary excretion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramethoprim</td>
<td>13.6 ± 2.0</td>
<td>1.9 ± 0.7</td>
<td>70.9 ± 11.1</td>
<td>13.6 ± 3.5</td>
<td>1.394 ± 0.254</td>
<td>1.227 ± 0.180</td>
<td>1.051 ± 0.256</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>372 ± 64</td>
<td>2.6 ± 1.0</td>
<td>2.059 ± 351.1</td>
<td>14.0 ± 2.3</td>
<td>0.249 ± 0.046</td>
<td>0.211 ± 0.033</td>
<td>0.024 ± 0.009</td>
</tr>
<tr>
<td>N4-acetylsulfamethoxazole</td>
<td>50.1 ± 10.9</td>
<td>2.8 ± 2.2</td>
<td>255.4 ± 39.1</td>
<td>18.6 ± 3.3</td>
<td>0.800 ± 0.280</td>
<td>0.800 ± 0.280</td>
<td>44 ± 11</td>
</tr>
</tbody>
</table>

a Data are mean values ± standard deviations. AUC and urinary excretion data are from 0 to 6 h after last dose. Abbreviations: T_{max}, time to achieve the maximum concentration of drug in serum; T_{1/2}, terminal-phase half-life; V/F, apparent volume of distribution; CL/F, total apparent oral clearance; CL_{ur}, renal clearance.

### Table 2. Adverse reactions from trimethoprim-sulfamethoxazole

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Total no. of doses received</th>
<th>Cumulative dose (g) of TMP/SMX</th>
<th>Adverse reactionsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects completing study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>13</td>
<td>4.7/23.4</td>
<td>GI, CNS, ↑ serum transaminase</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
<td>5.2/26.0</td>
<td>GI, CNS, ↑ serum transaminase, ↓ leukocytes, ↓ neutrophils</td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>5.2/26.0</td>
<td>GI, CNS</td>
</tr>
<tr>
<td>8</td>
<td>13</td>
<td>5.2/26.0</td>
<td>GI, CNS, hypoglycemia, ↑ lactate dehydrogenase</td>
</tr>
<tr>
<td>9</td>
<td>13</td>
<td>4.2/20.8</td>
<td>GI, CNS</td>
</tr>
<tr>
<td>10</td>
<td>13</td>
<td>5.7/28.6</td>
<td>GI, CNS</td>
</tr>
<tr>
<td>12</td>
<td>13</td>
<td>5.7/28.6</td>
<td>GI, CNS, ↓ hearing, disorientation</td>
</tr>
<tr>
<td>Subjects discontinued study because of toxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>2.8/14.0</td>
<td>GI, CNS, emesis, hypoglycemia, ↑ serum transaminase, ↑ lactate dehydrogenase, ↓ leukocytes, ↓ neutrophils</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>4.0/19.8</td>
<td>GI, CNS, emesis 3 times, diarrhea, hypoglycemia, ↑ serum transaminase, ↑ lactate dehydrogenase</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>3.1/15.4</td>
<td>GI, CNS, emesis 2 times, hypoglycemia, ↓ leukocytes</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>2.6/12.8</td>
<td>GI, CNS, emesis 4 times, hypoglycemia, ↓ leukocytes</td>
</tr>
<tr>
<td>11</td>
<td>8</td>
<td>2.6/12.8</td>
<td>GI, CNS, ↓ hearing, disorientation, ↓ neutrophils, ↓ lactate dehydrogenase</td>
</tr>
</tbody>
</table>

a Subjects received 5 mg of trimethoprim and 25 mg of sulfamethoxazole per kilogram orally every 6 h.

b TMP, trimethoprim; SMX, sulfamethoxazole.

c The following gastrointestinal (GI) and CNS adverse reactions were experienced by all subjects: GI, nausea and anorexia; CNS, headache, nervousness, fine tremors, lightheadedness, insomnia, and drowsiness. Hypoglycemia, blood glucose level of <60 mg/dl; ↑ serum transaminases (alanine aminotransferase and aspartate aminotransferase) and lactate dehydrogenase, ≥1.5-fold increase from baseline value; leukocytes and neutrophils, decrease of ≥1,000 cells per mm³ from baseline value.
count in five subjects decreased by ≥1,000 cells per mm³ (mean, 1,800 ± 640 cells per mm³; decrease of 11 to 39%). The ANC dropped by ≥1,000 cells per mm³ in three subjects (mean, 1,579 ± 499 cells per mm³; decrease of 27 to 54%). None of the subjects were symptomatic from any change in the hematologic or blood chemistry profiles.

**DISCUSSION**

Our findings describe the disposition of trimethoprim, sulfamethoxazole, and N-acetylsulfamethoxazole following conventional pneumocystis pneumonia dosing with trimethoprim-sulfamethoxazole in adults. The 12 healthy adult subjects that participated in this study had high serum drug concentrations of trimethoprim and sulfamethoxazole. The steady-state Cmax of trimethoprim and sulfamethoxazole in the seven subjects completing the study were at least two-fold greater than the 5 to 8 µg/ml range for trimethoprim that is associated with therapeutic efficacy of PCP in adults (19) or the peak (2 h after oral dose) serum drug concentrations of trimethoprim (3 to 5 µg/ml) and sulfamethoxazole (100 to 150 µg/ml) in children (10). The results of our study are in agreement with the data of Lee et al. (16) and Medina et al. (17) in which 30 patients with AIDS were treated orally with the conventional dose of trimethoprim-sulfamethoxazole for PCP. In 11 patients from these studies (16, 17), in which serum drug concentrations were determined at steady state, the peak values (mean ± standard deviation, with the range given in parentheses) (2 h after oral dose) of serum drug concentrations were 12.4 ± 4.5 (8.2 to 20.7), 284 ± 70 (195 to 416), and 32.5 ± 13.4 µg/ml (19.1 to 69.9 µg/ml) for trimethoprim, sulfamethoxazole, and N-acetylsulfamethoxazole, respectively. These values are comparable with the steady-state serum drug concentrations at the 2 h time point in this study for trimethoprim (12.8 ± 1.7 µg/ml; range, 10.0 to 14.6), sulfamethoxazole (351 ± 67 µg/ml; range, 261 to 469), and N-acetylsulfamethoxazole (42.5 ± 6.5 µg/ml; range, 35.7 to 53.2).

Multiple studies of trimethoprim-sulfamethoxazole use in adult AIDS patients with PCP have used the dose of 20 mg/kg/day trimethoprim and 100 mg/kg/day sulfamethoxazole (1, 9, 12, 17, 23). The rationale for widespread use of this conventional trimethoprim-sulfamethoxazole dose in adults is not substantiated, since this dosing regimen originated from the reports by Hughes et al. (10, 11) for pediatric cancer patients. Age-related variables that affect drug disposition have been reported with numerous agents, including the sulfonamides (18). As a result, extrapolation of a milligram-per-kilogram dose from children to adults may lead to excessive serum drug concentrations of certain agents and result in an increased incidence of concentration-dependent toxicities as observed in this and other studies (5, 16, 17, 19).

A lower milligram-per-kilogram dose of trimethoprim-sulfamethoxazole in adults compared with children can be rationalized on the basis of age-related differences in drug disposition. Siber and associates (22) described several pharmacokinetic indices that differed between pediatric and adult patients receiving intravenous trimethoprim-sulfamethoxazole. The daily dose needed to attain trimethoprim Cmax values of 5 to 10 µg/ml in nine children (age, 1 to 9 years) was 20 mg of trimethoprim and 100 mg of sulfamethoxazole per kg compared with 12.5 and 62.5 mg/kg, respectively, in five adult patients (age, 20 to 63 years). The volumes of distribution were larger in children compared with adults (trimethoprim, 1.64 versus 1.36 liter/kg, respectively; sulfamethoxazole, 0.47 versus 0.35 liter/kg, respectively). The distribution volumes in the five adult patients are similar to the volumes reported in the seven healthy subjects in this study. Only patients less than 10 years of age in Siber et al.'s study received the conventional dose of trimethoprim-sulfamethoxazole recommended for treatment of PCP. The need for a smaller milligram-per-kilogram dose in adults to attain comparable serum drug concentrations as in children may be explained, in part, by smaller distribution volumes in the former population. However, since the investigators did not report clearance values in their study (22), correlations that explain the need for smaller doses in adults cannot be definitively established. Similarly, Winston et al. (24) did not need to give dosages in excess of 15-mg/kg/day trimethoprim and 75-mg/kg/day sulfamethoxazole in adult immunocompromised cancer patients to achieve serum trimethoprim concentrations of ≥5.0 µg/ml. Sattler and colleagues (19) in a study of 36 AIDS patients reported that a mean daily intravenous dose of 15 ± 27 mg/kg could be reduced to 12 ± 3.4 mg/kg for the trimethoprim component to maintain therapeutic serum trimethoprim concentrations between 5 and 8 µg/ml. The results of these three studies (19, 22, 24) along with our data are evidence supporting further investigation of using a lower dose of trimethoprim-sulfamethoxazole in adults to effectively treat PCP.

The adverse effects from trimethoprim-sulfamethoxazole observed in our subjects are significant (Table 2). Of 12 subjects, 5 withdrew from the study because of intolerable gastrointestinal and CNS toxicities. Toxicities affecting the CNS were not predicted, since only one patient from the large numbers of patients collectively studied that received >15-mg/kg/day trimethoprim and >75-mg/kg/day sulfamethoxazole (1, 6, 9, 12, 15, 17, 19, 20, 23) developed CNS toxicity, which was manifested as a change in mental status. The CNS toxicities most plaguing to our subjects were fine tremors, headache, and nervousness. It is unclear why our subjects experienced the types and frequency of CNS adverse effects. Although the serum trimethoprim-sulfamethoxazole concentrations were well beyond the therapeutic range for treating PCP, the concentrations were not substantially higher compared with those of other studies using conventional pneumocystis pneumonia dosing in adult AIDS patients. Because of the nonblinded nature of this study, caution must be exercised in the interpretation of the frequency of subjective complaints reported by the subjects. However, clinicians should be sensitive to potential CNS toxicities from high-dose trimethoprim-sulfamethoxazole therapy, since these adverse effects may be underreported.

Statistically significant correlations were demonstrated between the change in ANC and trimethoprim Cmin, sulfamethoxazole Cmin and trimethoprim AUC. We were unable to describe any significant correlation between ANC and Cmax. The inverse relationship between ANC with Cmin and AUC suggests that total systemic exposure to trimethoprim-sulfamethoxazole is more predictive of changes in neutrophil count than peak drug concentrations. These relationships were characterized despite the study being biased against finding toxicity, since posttreatment laboratory studies were not obtained until 72 h after the last scheduled dose of trimethoprim-sulfamethoxazole. The fact that our healthy subjects manifested signs of bone marrow suppression after 3 days of drug administration that persisted 72 h after their last dose is surprising. Feldman and colleagues reported that ANCs of <1,500 cells per mm³ occurred transiently in 57% of 49 children receiving trimethoprim-sulfamethoxazole therapy for otitis media but this incidence was no different
than in the group receiving amoxicillin (4). Our findings add to the evidence that some of the toxicities of trimethoprim-sulfamethoxazole are concentration dependent. In a recent study by Fong (5), a statistically significant lower incidence of leukopenia and neutropenia was shown in AIDS patients when peak sulfamethoxazole concentrations were <200 μg/ml. None of the 36 AIDS patients receiving trimethoprim-sulfamethoxazole therapy reported by Sattler et al. (19) had significant toxicity when dosages were adjusted to maintain trimethoprim concentrations of 5 to 8 μg/ml.

A major pathway of sulfonamide metabolism is N-acetylation, which is mediated by a polymorphic hepatic enzyme, N-acetyltransferase. The effect of the acetylated metabolite in the treatment of pneumocystis pneumonia is unknown, but knowing the concentration of this product can provide information that could be useful in assessing drug toxicity.

Shear and colleagues (21) have shown that sulfonamides are oxidatively metabolized to a toxic hydroxylamine intermediate metabolite which is responsible for causing idiosyncratic reactions, including bone marrow suppression and hepatotoxicity. Susceptibility to these toxicities was shown to be caused by differences in the rate of acetylation of the parent sulfamethoxazole and by the rate of production of the toxic intermediate and its detoxification by conjugation. Our pharmacokinetic study did not assess the polymorphic metabolism of sulfamethoxazole. However, the peak concentrations of N'-acetylsulfamethoxazole in the serum samples of our healthy subjects as illustrated in Fig. 1 do not significantly differ from the values reported by Lee et al. for 11 AIDS patients (16). Detailed studies that characterize sulfamethoxazole metabolism in AIDS compared with non-AIDS individuals are needed to see whether differences exist.

The pharmacokinetic parameters determined in this study provide useful information for developing dosing strategies for treatment of PCP in adults. The trimethoprim and sulfamethoxazole concentrations in serum maintained throughout the 6-h dosing interval significantly exceed concentrations reported to be efficacious in both AIDS and non-AIDS immunocompromised patients with various degrees of severity of pneumonia. As depicted in Fig. 1, the concentrations of trimethoprim and sulfamethoxazole at 24 h after drug administration had been discontinued are within the lower limits of the desired peak concentrations. The average half-lives of approximately 14 h indicate that dosing intervals can be increased to at least every 8 h. The C_{min} data presented in Fig. 2 show that 10 of the 11 subjects at the end of 24 h of receiving 20-mg/kg/day trimethoprim and 100-mg/kg/day sulfamethoxazole attained concentrations within the proposed therapeutic range of 5 to 8 μg/ml for trimethoprim (19). The one exception was a trimethoprim C_{min} value of 4.8 μg/ml. As a result, clinical trials are justified to evaluate the efficacy and toxicity of a loading dose regimen of trimethoprim-sulfamethoxazole using the conventional dose for the first 36 h followed thereafter by a reduced (i.e., 12-mg/kg/day trimethoprim and 60-mg/kg/day sulfamethoxazole) maintenance dose. By using the mean clearance values listed in Table 1 and data presented by Sattler et al. (19), a reduced maintenance dose of 12-mg/kg/day trimethoprim and 60-mg/kg/day sulfamethoxazole would be predicted to yield steady-state serum drug concentrations within the therapeutic range. This dosing scheme should result in a rapid and uniform attainment of therapeutic concentrations compared with an initial dose of 15-mg/kg/day trimethoprim and 75-mg/kg/day sulfamethoxazole (19) with less need for pharmacokinetic monitoring. The relationship between neutrophil counts and trimethoprim-sulfamethoxazole systemic drug exposure indicate that reduced-dose regimens could decrease this concentration-dependent toxicity. Further investigations to evaluate reduced doses of trimethoprim-sulfamethoxazole are needed to better describe the therapeutic index of this drug for treating PCP.

In summary, the dose of 20-mg/kg/day trimethoprim and 100-mg/kg/day sulfamethoxazole extrapolated from the pediatric population produces serum drug concentrations in adults that are at least twofold higher than the proposed therapeutic range for the treatment of PCP. Concentrations achieved from this conventional pneumocystic pneumonia dose accounted for significant toxicity in our healthy subjects. Additional studies are indicated to optimize the dose of trimethoprim-sulfamethoxazole, which remains a mainstay of the armamentarium used in the drug therapy of PCP.

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