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Pharmacokinetics of Trimethoprim-Sulfamethoxazole in Critically Ill and Non-Critically Ill AIDS Patients

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Current dosage regimens of trimethoprim-sulfamethoxazole used to treat *Pneumocystis carinii* pneumonia in AIDS patients have been based on data from healthy subjects or patients without AIDS. The clearance and absorption characteristics of the drugs may potentially be different between patients with and without AIDS. This study was conducted to assess the pharmacokinetics of trimethoprim-sulfamethoxazole in critically ill and non-critically ill AIDS patients treated for *P. carinii* pneumonia. Patients received trimethoprim at 15 mg/kg of body weight and sulfamethoxazole at 75 mg/kg of body weight daily intravenously in three to four divided doses and were switched to the oral route when the regimen was tolerated. Serum samples for determination of drug concentrations were obtained over 12 h after intravenous and oral dosing. The pharmacokinetics of trimethoprim and sulfamethoxazole were compared in eight critically ill versus nine non-critically ill male patients and were as follows, respectively: clearance, 1.88 ± 0.44 versus 1.73 ± 0.64 ml/min/kg for trimethoprim and 0.40 ± 0.12 versus 0.34 ± 0.11 ml/min/kg for sulfamethoxazole; volume of distribution, 1.6 ± 0.5 versus 1.5 ± 0.5 liters/kg for trimethoprim and 0.5 ± 0.3 versus 0.4 ± 0.1 liters/kg for sulfamethoxazole; and half-life, 10.9 ± 7.4 versus 11.3 ± 4.0 h for trimethoprim, and 15.5 ± 9.5 versus 14.3 ± 4.7 h for sulfamethoxazole. No significant differences ($P > 0.05$) were observed between patient groups, although there was wide intersubject variability. Absorption appeared to be similar between the critically ill and non-critically ill patients: bioavailability was 97.5% ± 22.4% versus 101.8% ± 22.7% for trimethoprim and 86.2% ± 17.9% versus 99.1% ± 20.5% for sulfamethoxazole, respectively. Because of the similar pharmacokinetics of trimethoprim-sulfamethoxazole in critically ill and non-critically ill AIDS patients, the two groups of patients may receive similar dosages. Dosage adjustment does not appear to be required when switching from the intravenous to the oral route.

Pneumocystis carinii pneumonia (PCP) remains a prevalent life-threatening opportunistic infection in patients with AIDS, although the incidence is declining since the introduction of chemoprophylaxis (19). Trimethoprim-sulfamethoxazole (or co-trimoxazole) is one of several drug regimens available for the treatment of PCP. All of the regimens have been associated with a high incidence of adverse effects. Despite the greater incidence of toxicity observed in AIDS patients (6, 8, 13, 17, 29), co-trimoxazole remains a primary agent of choice for treating PCP.

The current dosage recommendations for trimethoprim-sulfamethoxazole from various reference texts as well as from the manufacturers are 20 and 100 mg/kg of body weight daily, respectively, for the treatment of PCP. The rationale for the widespread use of this conventional dosage in adults has not been substantiated by detailed pharmacokinetic studies in adult AIDS patients. The dosage was originally established by Hughes et al. (10, 11) for pediatric cancer patients and was subsequently extrapolated to the adult patient population (6, 8, 13, 17, 23, 29). Age-related variables that affect the dispositions of numerous agents have been reported (18, 25). Siber et al. (25) reported that pediatric patients tend to have larger volumes of distribution and shorter elimination half-lives of trimethoprim-sulfamethoxazole than adults. As a result, extrapolation of a milligram-per-kilogram dose from children to adults may lead to excessive serum drug concentrations because of disparities in drug dispositions between the two patient populations. Several studies reported excessive toxic concentrations of trimethoprim (peak, >8 μg/ml) and sulfamethoxazole (peak, >200 μg/ml) when the conventional dosage was prescribed for PCP in AIDS patients (4, 15, 23, 25–27).

The use of the conventional dosage and the resulting high concentrations in serum may be a contributing factor in the increased incidence of the concentration-dependent toxicities observed in AIDS patients. On the basis of the experience at our institution (4, 5) and the study of Sattler et al. (23), the dosage of co-trimoxazole for the initiation of therapy has been empirically reduced to approximately 15 mg of trimethoprim per kg and 75 mg of sulfamethoxazole per kg daily. The dosage is subsequently adjusted, if necessary, to maintain serum drug concentrations in the range of 5 to 8 μg/ml for trimethoprim and 100 to 200 μg/ml for sulfamethoxazole (4, 5, 15, 23). However, to date the detailed pharmacokinetics of trimethoprim-sulfamethoxazole have not been adequately characterized in patients with AIDS. Information on the pharmacokinetics have been obtained primarily from studies in healthy subjects or in patients without AIDS or from studies of diseases other than PCP conducted with lower doses (9, 10, 20, 25–27). Previous studies of trimethoprim-sulfamethoxazole concentrations in AIDS patients have been limited to measurement of peak and trough concentrations in serum (1, 4, 15, 23). Moreover, the absorption characteristics of co-trimoxazole when it is administered orally are not established within the dosage range used to treat PCP. Many patients with PCP are critically ill, and it is not clear if the pharmacokinetics of co-trimoxazole are altered in these patients. Therefore, to have a better understanding of the dose-concentration relationship

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and the absorption characteristics of trimethoprim-sulfamethoxazole, a study was conducted to characterize the detailed pharmacokinetics of co-trimoxazole. Since a number of AIDS patients with PCP could often be severely ill on admission into the hospital, both critically ill and non-critically ill patients were studied. The objectives of the present study were therefore to determine and compare the pharmacokinetic parameters of intravenously and orally administered trimethoprim and sulfamethoxazole in both critically ill and non-critically ill AIDS patients being treated for PCP.

MATERIALS AND METHODS

Patients. A total of 24 human immunodeficiency virus (HIV)-positive patients with AIDS admitted to the hospital for the treatment of presumptive or proven pneumonia caused by *P. carinii* were enrolled in the study. The patients gave informed consent, which was approved by St. Michael's Hospital's Research Ethics Committee. Patients were divided into two groups of 12 patients each, critically ill and non-critically ill patients. The patients were defined as critically ill if they required admission into the critical care unit for mechanical ventilation for the management of respiratory failure. The non-critically ill patients had only mild to moderate respiratory distress and were managed adequately with oxygen therapy via mask or nasal prong as required. The severity of the patient's illness was classified according to the APACHE II scoring system (12), as well as the baseline arterial O_2 pressure (PaO_2).

Each patient underwent a medical history, a physical examination, and laboratory evaluation prior to the initiation of the study. A definitive diagnosis of PCP was established by clinical or radiological evidence of pneumonia plus a smear from a sputum, bronchial lavage, or transbronchial biopsy specimen positive for the *P. carinii* organism. A presumptive diagnosis was made on the basis of clinical or radiological evidence of diffuse interstitial pneumonia, but without positive identification of the organism either because an inadequate amount of specimen was obtained or because of an inability to perform the procedure, and no other microorganism was identified. Laboratory tests were generally repeated at least once and three times weekly for the non-critically ill and critically ill patients, respectively. These tests included complete blood count with differential and serum creatinine, liver enzyme, and bilirubin level determinations. Patients were also monitored for the occurrence of nausea, vomiting, abdominal pain, phlebitis, and rash. Patients were discontinued from the study for the following reasons: intolerance to trimethoprim-sulfamethoxazole because of adverse reactions such as severe rash, hematologic, liver, or renal toxicity, the diagnosis was confirmed not to be PCP, and voluntary withdrawal.

Drug administration. Patients were initiated on 15 mg of trimethoprim per kg/day and 75 mg of sulfamethoxazole per kg/day administered intravenously or orally in three to four divided doses. After the intravenous or oral pharmacokinetic study was conducted, patients were switched to receive the equivalent dosage by the alternate route. Treatment of critically ill patients was usually initiated by the intravenous route, and they were switched to the oral route only when they were able to tolerate oral intake; patients who could not swallow tablets were administered an oral suspension via a nasogastric tube. Since each ampoule, suspension, or tablet contained a specific amount of drug, each dose was rounded to the nearest convenient dosage form. Each intravenous test dose was diluted in normal saline or 5% glucose in water solution in a 1:15 dilution and was infused over 30 min. Following administration of the suspension, the nasogastric tube was completely flushed with water and was clamped for at least half an hour. Critically ill patients who were on enteral feeding had their feeds held while the nasogastric tube was clamped. Studies were generally conducted under nonfasting conditions except for those in which intravenous doses were administered to critically ill patients.

Sample collection. Blood samples were obtained for the intravenous and oral pharmacokinetic studies between days 2 and 10 after the initiation of treatment by the respective route. Prior to administration of the test dose, an indwelling intravenous catheter was inserted into a forearm vein contralateral to the arm used for drug infusion. In the critically ill patients, blood samples were obtained via the arterial line inserted for other critical care management purposes. A heparin solution of 100 IU/ml was used to maintain the patencies of both types of catheters. The initial 2 to 3 ml of blood was discarded prior to obtaining each sample. Blood samples (7 ml) were obtained in plain red-top evacuated tubes before the administration of a morning test dose at the following times: before and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 h after dose administration. Blood sampling was repeated for each patient after the route of administration was switched to the alternate route. The next scheduled dose subsequent to administration of the test dose was held until 12 h after all samples were collected. All samples were centrifuged, and the serum was stored at −70°C until it was assayed.

Drug analysis. The concentrations of trimethoprim and sulfamethoxazole in serum were analyzed by a high-pressure liquid chromatography technique based on a modification of the technique developed by Weber and Opheim (28). The limits of detectability for this assay were as follows: trimethoprim, 1.5 μg/ml; sulfamethoxazole, 1.5 μg/ml. The linearity of the assay with a 5-μl injection is at least 150 μg/ml for trimethoprim and 350 μg/ml for sulfamethoxazole. The within- and between-day assay coefficients of variation for trimethoprim at concentrations of 5 and 35 μg/ml were 13 and 7%, respectively; for sulfamethoxazole the coefficients of variation were 12 and 8% at concentrations of 10 and 175 μg/ml, respectively.

Data analysis. From the serum concentration-time data, pharmacokinetic parameters were determined by standard noncompartmental techniques (7). The elimination rate constant (k_{el}) was estimated from the terminal linear portion of the serum drug concentration-time profile by using weighted nonlinear least-squares regression analysis (PCNONLIN). The elimination half-life ($t_{1/2}$) was calculated by dividing the natural logarithm of 2 by k_{el}. The area under the serum concentration-time curve (AUC) during a steady-state dosing interval was estimated by the linear trapezoidal method from time zero to the end of the dosing interval following the test dose. Total drug clearance (CL) was calculated from the dose divided by AUC. The volume of distribution (V) was determined by dividing CL by k_{el}. CL, V, and $t_{1/2}$ were determined only from the data obtained from patients given the drug by the intravenous route. The absolute oral bioavailability (f) of the tablet or suspension was determined by dividing the AUC of the oral dose by the AUC of the intravenous dose. The maximum concentration (C_{max}) and the time to attain C_{max} (T_{max}) were estimated by visual inspection of the serum concentration-time profile. Data are reported as means ± standard deviations (SDs) unless indicated otherwise. Individual demographic parameters between critically ill and non-critically ill patients were compared by Student's t test. Student's t test (unpaired) was used to assess differences in the following pharmacokinetic parameters between critically ill and non-critically ill patients: $t_{1/2}$, V, CL, T_{max}, and f. The AUC between intravenous and oral doses within each patient group was compared by paired Student's t test to determine if the two formulations had equivalent bioavailabilities. Two-way analysis of variance was used to compare C_{max} between patient groups and treatment routes, with the Scheffe's multiple comparison test used if a significant difference was detected. A probability value of less than 0.05 was considered statistically significant.

RESULTS

A total of eight critically ill and nine non-critically ill male patients were studied. The remaining seven patients were excluded because of poor venous access, an inability to maintain the patency of the venous catheter after study initiation, or voluntary withdrawal because of apprehension or apathy. All patients had a diagnosis of AIDS according to the classification of the Centers for Disease Control and Prevention (3). Except for the baseline PaO_2 level, APACHE II score, and lactate dehydrogenase (LDH) level, there was no significant difference in the demographic features between the patient groups (Table 1). Serum biochemical parameters were generally within normal limits or, if they were elevated, were not more than two times above the normal limits for most patients. The higher mean APACHE II scores and lower PaO_2 values in critically ill patients indicated the greater severity of their illness. LDH values were significantly elevated in the critically ill patients, but they were available from only three patients. In the non-critically ill patients, LDH levels were elevated in four patients but were significantly elevated in only one patient. Except for two patients, one in each group, all patients had either a confirmed diagnosis of PCP ($n = 11$) or a presumptive diagnosis of PCP on the basis of clinical and radiological evidence ($n = 4$); one critically ill patient had mycobacterial pneumonia, while one non-critically ill patient most likely had community-acquired bacterial pneumonia.

Plots of the mean serum drug concentration-time profiles for trimethoprim and sulfamethoxazole after intravenous administration to critically ill and non-critically ill patients are presented in Fig. 1 and 2, respectively. Results of noncompartmental pharmacokinetic analyses for the two compounds in both groups of patients are summarized in Table 2. All except one of the non-critically ill patients were assessed after intravenous and oral dosing; one patient died before the pharmacokinetics after oral dosing could be assessed. Pharmacokinetics after oral dosing could be assessed in only four critically ill patients; two of these patients received the oral suspension,

TABLE 1. Demographics of study patients[a]

Parameter	Critically ill (n = 8)	Non-critically ill (n = 9)
Age (yrs)	37 ± 8	37 ± 9
Wt (kg)	68.5 ± 12.0	67.6 ± 10.8
Race or ethnic group (no.)		
Black	2	1
White	6	8
PaO_2 (mm Hg)	48.3 ± 10.0[b]	71.9 ± 9.8[b]
APACHE II score	20 ± 2.4[b]	11.1 ± 2.4[b]
CD4 lymphocyte cell count (cells/mm^3)	43.9 ± 41.1 (7)	110.0 ± 87.3 (7)
Serum creatinine level (μmol/liter)	62.3 ± 37.4 (8)	86.7 ± 21.7 (9)
Alanine aminotransferase level (U/liter)	25.5 ± 10.8 (6)	92.3 ± 111.9 (7)
Aspartate aminotransferase level (U/liter)	28.6 ± 11.9 (8)	27.9 ± 12.9 (9)
Alkaline phosphatase level (U/liter)	155.0 ± 127.7 (6)	63.4 ± 21.6 (9)
Total bilirubin level (μmol/liter)	30.1 ± 33.3 (7)	8.9 ± 3.5 (7)
LDH level (U/liter)	455.5 ± 226.9 (3)[c]	187.6 ± 94.3 (7)[c]

[a] Data are mean ± SDs. Numbers in parentheses refer to the number of patients for whom test results were available.
[b] $P < 0.001$.
[c] $P < 0.05$.

while the other two patients received the tablet. Because of the small sample size, the data for both the suspension and the tablet were grouped for analysis. This was based on the assumption that the suspension and tablet forms have similar bioavailabilities (14). In the four critically ill patients who completed only the intravenous study, one was diagnosed with mycobacterial pneumonia, while the other three died. Three of 17 intravenous dose studies and five of 12 oral dose studies in all patients were conducted prior to attaining steady state after switching to the alternate route. However, when the initial concentrations and the concentrations at the end of the dosing interval were compared for all patients by a paired t test, there was no significant difference. The pharmacokinetics of trimethoprim-sulfamethoxazole between the critically ill and non-critically ill patients were not significantly different ($P > 0.05$) on the basis of comparison of $t_{1/2}$, V, CL, C_{max}, T_{max}, and f. Within each patient group, the f of trimethoprim-sulfamethoxazole administered orally appeared to be comparable to that of the drugs administered intravenously (Table 2). Wide interpatient variability in these parameters was observed.

All patients tolerated both the intravenous and the oral doses studied. No patient withdrew from the study because of adverse effects such as phlebitis, nausea, vomiting, dizziness, headache, or hypersensitivity reactions. In addition, there was no exacerbation of hematologic or blood biochemical parameters. The patients were not receiving any drugs known to significantly interact with the pharmacokinetics of trimethoprim or sulfamethoxazole.

DISCUSSION

Pharmacokinetic characterization of trimethoprim-sulfamethoxazole that specifically pertains to AIDS patients has been unavailable in the literature, despite the widespread use of the drugs for the treatment of PCP. Current trimethoprim-sulfamethoxazole dosage recommendations for the treatment of PCP have been extrapolated from data obtained from pediatric patients (10, 11). Detailed pharmacokinetic studies have been conducted only in healthy adult volunteers or in patients with immunosuppression caused by an illness other than AIDS (9, 25–27). Our study characterized the detailed pharmacokinetics of trimethoprim-sulfamethoxazole at the dosages used to treat PCP in AIDS patients.

Our findings demonstrate that the disposition of trimethoprim-sulfamethoxazole is similar between critically ill and non-critically ill AIDS patients (Fig. 1 and 2; Table 2). Mean C_{max} values at steady state were within the therapeutic range of 5 to 8 μg/ml for trimethoprim and 100 to 200 μg/ml for sulfamethoxazole in both critically ill and non-critically ill patients (Table 2). C_{max} generally occurred within 2 h after oral administration (Table 2). In non-critically ill patients, both agents appeared to be well absorbed when they were administered orally, with f being equivalent to that of the intravenous formulation (Table 2). Thus, therapy in non-critically ill patients may generally be initiated by the oral route if it can be tolerated. In the critically ill patients, the f of orally administered trimethoprim-sulfamethoxazole also appeared to be similar to that of the intravenous formulation (Table 2); however, this conclusion was based on data from only four patients. It would also appear to be possible that when critically ill patients are initiated on trimethoprim-sulfamethoxazole intravenously,

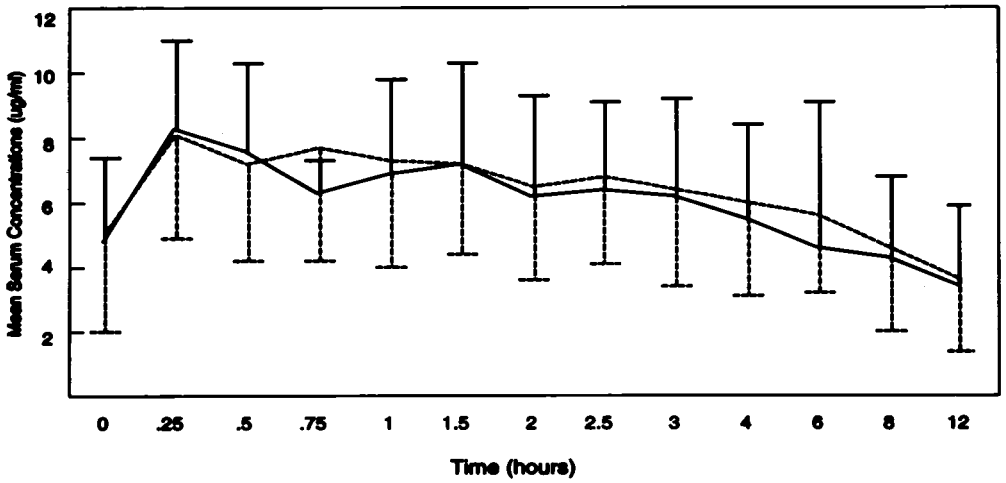

FIG. 1. Mean ± SD trimethoprim concentrations in serum after intravenous administration to critically ill patients (——) and non-critically ill patients (– – – –).

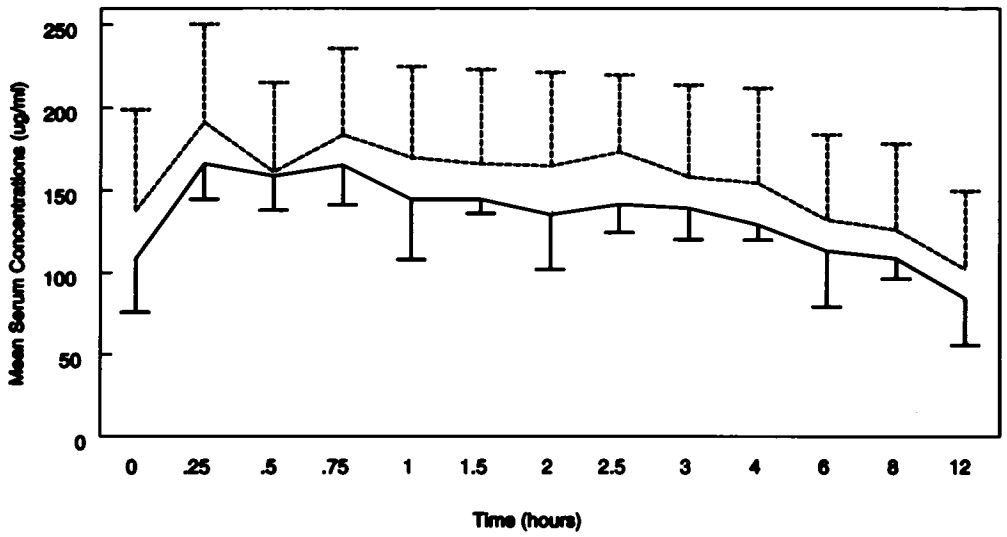

FIG. 2. Mean ± SD sulfamethoxazole concentrations in serum after intravenous administration to critically ill patients (——) and non-critically ill patients (– – – –).

they may be switched to the oral formulation when they have been clinically stabilized and are able to tolerate oral feeds. The fact that the patient is in an intensive care unit does not preclude him or her from being administered the oral formulation, which represents a more cost-effective measure since the intravenous injection is approximately 16 and 70 times more expensive than the suspension and tablet forms, respectively. It should also be noted that because critically ill patients always received the drug intravenously before receiving it orally, the possibility of a period effect that may influence the results exists. However, no significant difference in the AUC was observed between the intravenous and oral doses, and there are no known data in the literature that suggest that the elimination or distribution of trimethoprim-sulfamethoxazole might be affected by the formulation or route of administration.

The detailed pharmacokinetics of trimethoprim-sulfamethoxazole studied with two different PCP doses were only recently reported by Stevens et al. (26, 27). However, those investigators evaluated the pharmacokinetics of only the orally administered tablets and conducted the studies in healthy subjects without HIV infection. They found that the pharmacokinetics of trimethoprim and sulfamethoxazole were similar when they were administered at two doses, 20 and 100 mg/kg daily versus 12 and 60 mg/kg daily, respectively. T_{max} ranged from 1.5 to 1.9 h for trimethoprim and 1.8 to 2.6 h for sulfamethoxazole (26, 27), which were similar to our findings (Table 2). The mean elimination $t_{1/2}$ ranged from 13.6 to 14.6 h for trimethoprim and was 14 h for sulfamethoxazole. Those investigators (26, 27) also reported that the mean oral CL and V of trimethoprim ranged from 1.23 to 1.43 ml/min/kg and 1.4 to 1.8 liter/kg, respectively. For sulfamethoxazole, the mean oral CL and V were 0.21 to 0.23 ml/min/kg and 0.25 to 0.27 liter/kg, respectively. Because the studies evaluated the pharmacokinetics of drugs administered orally only, these values are considered "apparent." In a recent study in trauma patients (9), mean elimination $t_{1/2}$s of trimethoprim and sulfamethoxazole were 9.8 and 8.4 h, respectively, while mean CL values were 2.8 and 0.75 ml/min/kg, respectively, and values of V were 2.1 and 0.5 liters/kg, respectively. Much earlier studies (20, 25) have also reported elimination $t_{1/2}$s of 8 to 11 h in non-HIV-infected subjects and values of V of 1.36 and 0.35 liters/kg for trimethoprim and sulfamethoxazole, respectively. In general, the values of V, CL, and elimination $t_{1/2}$ of trimethoprim and sulfamethoxazole among the various studies are probably not significantly different, although trauma patients seem to have somewhat higher values of CL for trimethoprim and sulfamethoxazole and larger values of V for trimethoprim. Any observed differences in the pharmacokinetic parameters reported among the various studies, including our study, may be related to the different subject populations as well as study methodologies, such as a relatively small sample size, pharmacokinetics of orally versus intravenously administered drug, and drug assay techniques.

The relationships between trimethoprim-sulfamethoxazole concentrations or dosage versus therapeutic efficacy or toxicity have not been precisely defined and remain controversial. However, several studies have provided some evidence suggesting that excessive drug concentrations in serum may result in increased incidences of concentration-dependent toxicities. Sattler and colleagues (23), in a study of 36 AIDS patients, reported that a mean daily intravenous dosage of 12 ± 3.4 mg of trimethoprim per kg produced serum trimethoprim concentrations of between 5 and 8 μg/ml, which resulted in decreased drug toxicity without an apparent diminution in efficacy. The dosage was adjusted to maintain these concentrations by measurement of samples at 0.5 h before and 1.5 h after the end of the intravenous infusion or oral ingestion. In a study of pediatric patients with leukemia treated for PCP, Hughes et al. (10, 11) reported that 2-h peak concentrations of 3 to 5 μg/ml for trimethoprim and 100 to 150 μg/ml for sulfamethoxazole were associated with therapeutic efficacy. Preliminary data from Fong (4) suggest that maintaining peak sulfamethoxazole concentrations at less than 200 μg/ml may decrease the incidence of leukopenia. We have subsequently reported in a study of 101 AIDS patients that treatment of PCP with 15 mg of trimethoprim per kg and 75 mg of sulfamethoxazole per kg daily was as efficacious as treatment with the conventional dosage of 20 mg of trimethoprim per kg and 100 mg of sulfamethoxazole per kg (5). However, patients in the lower-dose group, who had lower drug concentrations in their sera, had lower liver transaminase enzyme elevations ($P = 0.02$) and a trend toward

TABLE 2. Pharmacokinetic parameters of intravenously and orally administered trimethoprim and sulfamethoxazole[a]

Group	Dose-T (mg/kg/day)	Dose-S (mg/kg/day)	C_{max}-T (μg/ml)	C_{max}-S (μg/ml)	$t_{1/2}$-T (h)	$t_{1/2}$-S (h)	Vd-T (L/kg)	Vd-S (L/kg)	Cl-T (mL/min/kg)	Cl-S (mL/min/kg)	T_{max}-T (h)	T_{max}-S (h)	*f*-T (%)	*f*-S (%)
Intravenous														
Critically ill ($n = 8$)	14.7 ± 2.1	73.4 ± 10.6	8.1 ± 2.6	163.6 ± 21.5	10.9 ± 7.4	15.5 ± 9.5	1.6 ± 0.5	0.5 ± 0.3	1.88 ± 0.44	0.40 ± 0.12				
Non-critically ill ($n = 9$)	16.1 ± 4.0	80.5 ± 19.9	7.9 ± 3.2	186.4 ± 59.9	11.3 ± 4.0	14.3 ± 4.7	1.5 ± 0.5	0.4 ± 0.1	1.73 ± 0.64	0.34 ± 0.11				
Oral														
Critically ill ($n = 4$)	15.1 ± 1.2	75.5 ± 6.0	6.6 ± 1.5	145.8 ± 42.0							1.3 ± 0.5	2.8 ± 2.4	97.5 ± 22.4	86.2 ± 17.9
Non-critically ill ($n = 8$)	16.0 ± 4.2	80.1 ± 21.1	8.3 ± 3.3	181.8 ± 74.7							1.8 ± 0.7	2.7 ± 1.5	101.8 ± 22.7	99.1 ± 20.5

[a] T, trimethoprim; S, sulfamethoxazole. Values are means ± SDs.

less leukopenia ($P = 0.06$). Further evidence exists to support the fact that the conventional dosage of trimethoprim-sulfamethoxazole produces excessive drug concentrations in serum. In 11 of 30 AIDS patients evaluated by Lee et al. (15) and Medina et al. (17), peak (2 h post-oral dosing) concentrations in serum were 12.4 ± 4.5 and 284 ± 70 μg/ml for trimethoprim and sulfamethoxazole, respectively. When Stevens et al. (27) evaluated the pharmacokinetics of the conventional dose of trimethoprim-sulfamethoxazole in healthy volunteers, 5 of 12 subjects withdrew from the study because of intolerable gastrointestinal and central nervous system toxicities. The investigators established an inverse relationship between a decreased absolute neutrophil count and total systemic drug exposure. Also, the conventional dosage produced mean C_{max} values of 13.6 ± 2.0 μg/ml at 1.9 ± 0.7 h postdosing for trimethoprim and 372 ± 64 μg/ml at 2.6 ± 1.0 h postdosing for sulfamethoxazole. In a subsequent study by the same investigators but with a lower daily dosage of 12 mg of trimethoprim per kg and 60 mg of sulfamethoxazole per kg, toxicities were not observed except for transient nausea, headache, tremors, and anxiety, and no subjects withdrew from the study (26). Not unexpectedly, this dosage produced lower mean C_{max} values of 8.3 ± 2.0 μg/ml at 1.5 ± 0.7 h postdosing for trimethoprim and 247 ± 52 μg/ml at 1.8 ± 0.5 h postdosing for sulfamethoxazole.

The cause of the increased frequency of side effects to trimethoprim-sulfamethoxazole in HIV-positive patients remains unclear. Besides dose or concentrations in serum, there may likely be other important factors that contribute to toxicity. Current hypotheses center around the role of slow acetylation, the formation of toxic reactive metabolites, in particular, hydroxylamine and nitroso compounds, and glutathione deficiency (2, 16, 21, 22, 24). Recently, Lee et al. (16) reported that AIDS patients with acute illness had an increased prevalence of apparent slow acetylation. However, this slow acetylation status was not found in stable AIDS patients or in HIV-infected patients without AIDS. Phenotyping of patients before treatment is initiated so that doses may be reduced in slow acetylators has been suggested (16), although the clinical application and usefulness of this technique remain to be established.

In conclusion, the pharmacokinetic characteristics of trimethoprim and sulfamethoxazole appear to be similar in critically ill and non-critically ill patients. Treatment in these patients with 15 mg of trimethoprim per kg and 75 mg of sulfamethoxazole per kg daily may be initiated. If the patient is initiated on the intravenous regimen, non-critically ill patients may be switched to the oral route when it is feasible without the need for dosage adjustment since the oral and intravenous formulations have comparable *f* values. On the basis of limited data, this also appears to be a feasible approach for critically ill patients, although this should be done only after the patient has been stabilized clinically and is able to absorb oral feeds. Because of the wide interpatient variability in trimethoprim-sulfamethoxazole pharmacokinetics observed in our study as well as other studies, use of any standard dosage regimen may result in some patients having excessive or subtherapeutic concentrations. Measurement of serum drug concentrations, if available, may be one way to adjust the dosage to maintain concentrations within the therapeutic range. Nevertheless, judicious monitoring of the patient's response and toxicity by measuring clinical and biochemical-hematological responses remains paramount in the treatment of PCP in AIDS patients.

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