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Multiple-Dose Pharmacokinetics of 12 Milligrams of Trimethoprim and 60 Milligrams of Sulfamethoxazole per Kilogram of Body Weight per Day in Healthy Volunteers

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The disposition of 12 mg of trimethoprim and 60 mg of sulfamethoxazole per kg of body weight in six healthy male volunteers is described. The daily dose was evenly divided and administered orally every 6 h for 13 consecutive doses. Individual drug components were assayed by high-performance liquid chromatography. Steady-state concentrations in serum for trimethoprim and sulfamethoxazole were within the purported therapeutic ranges for treating *Pneumocystis carinii* pneumonia. Co-trimoxazole was well tolerated, and no subject withdrew from the study because of toxicity. Comparison of the pharmacokinetic parameters in this study with those of our previous findings indicates that the elimination of trimethoprim-sulfamethoxazole follows a first-order process within the dose ranges assessed. Administration of 15- to 20-mg/kg trimethoprim and 75- to 100-mg/kg sulfamethoxazole in four evenly divided doses for the first 24 h followed by 12 and 60 mg/kg/day, respectively, for the remainder of therapy rapidly attains concentrations in serum within the proposed *P. carinii* pneumonia therapeutic range. Clinical trials are indicated to evaluate this dosing scheme, which may decrease exposure to potentially excessive concentrations of trimethoprim and sulfamethoxazole.

Pneumocystis carinii pneumonia (PCP) remains the most common life-threatening infection in patients with AIDS even though its incidence has been declining since the introduction of chemoprophylaxis (2). There are several treatment regimens currently in use for PCP, including trimethoprim-sulfamethoxazole, all of which are associated with a high incidence of adverse effects. Co-trimoxazole has remained a mainstay of therapy despite the high incidence of toxicity observed for AIDS patients (1, 5, 8, 11, 14, 21).

The conventional dose of 20 mg of trimethoprim and 100 mg of sulfamethoxazole per kg of body weight per day used for the management of PCP was originally established for pediatric oncology patients (9, 10) and subsequently extrapolated to the adult patient population (1, 5, 8, 11, 14, 17, 21). Pediatric patients have an increased volume of distribution and clearance of sulfonamides compared with adults (15, 18). As a result, excessive concentrations of trimethoprim-sulfamethoxazole in serum in adults caused by disparities in drug disposition compared with that of children occurred when the pediatric dose was extrapolated to adult AIDS patients. This could be a contributing factor in the increased incidence of concentration-dependent toxicities observed for the former population.

We have recently reported the pharmacokinetics of 20-mg/kg/day trimethoprim and 100-mg/kg/day sulfamethoxazole in the 7 of 12 healthy adult volunteer subjects who completed the study (20). The concentrations of trimethoprim and sulfamethoxazole in serum were excessive and resulted in toxicity related to systemic drug exposure (i.e., high area under the concentration-time curves and high trough serum drug concentrations). This is consistent with in vitro data in which trimethoprim and sulfamethoxazole each had concentration-dependent inhibition of hematopoiesis (7). Using data generated from the aforementioned report, we hypothesized that 12-mg/kg/day trimethoprim and 60-mg/kg/day sulfamethoxazole would result in concentrations in serum within the purported therapeutic range (5 to 8 μg/ml [17] or a concentration 2-h-post-oral dose of 3 to 5 μg/ml [9] for trimethoprim) for treatment of PCP. Therefore, this study was designed to characterize the pharmacokinetic parameters of 12-mg/kg/day trimethoprim and 60-mg/kg/day sulfamethoxazole in healthy volunteer subjects. Both clinical and laboratory assessments of drug toxicity were evaluated because of the low tolerability of co-trimoxazole in our previous trial (20).

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MATERIALS AND METHODS

Subjects and study design. Six healthy adult male subjects participated in this study after giving informed written consent. Each subject underwent a medical history, physical examination, and laboratory evaluation within 1 week prior to commencement of the study. Laboratory tests were repeated on study days 4 and 7. None of the subjects were smokers or were taking medication concurrent with the study. All subjects refrained from alcohol and caffeine products throughout the study.

As outpatients, subjects administered 3 mg of trimethoprim per kg and 15 mg of sulfamethoxazole per kg orally every 6 h for 13 consecutive doses (i.e., 3 days of dosing plus the first dose on day 4). Each dose was administered 1 h before or 2 h after meals. Following an overnight fast, the last dose was administered on the morning of day 4. Subjects continued to fast until 4 h postdose, after which a standard meal was provided. Single-strength tablets containing 80 mg of trimethoprim and 400 mg of sulfamethoxazole

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(lot OX2547 [Burroughs Wellcome Co., Research Triangle Park, N.C.]) were dispensed to the subjects for all doses. Since each tablet contained a specific amount of drug, each dose was rounded up to the nearest one-half tablet. Compliance was assessed by tablet counts and review of dosing time administration diaries maintained by each subject.

Sample collection. Blood samples (7 ml) were collected in plain red-top evacuated tubes before the 8:00 a.m. dose on days 1 to 3. Additional blood samples were collected prior to (0 h) and at the indicated times after the last dose (dose 13) on the morning of day 4: 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. Serum was harvested from each blood specimen after 15 min of centrifugation and stored at −70°C until assayed.

After voiding, urine was collected from each subject for 0 to 6 h (one dosing interval) after the last dose. The urine container was stored at 4°C during the 6-h collection period. Urine volumes were quantitated, and a 10-ml aliquot was frozen at −70°C until drug analysis.

Drug analysis. Trimethoprim, sulfamethoxazole, and N^4-acetylsulfamethoxazole concentrations in serum and urine were determined by using an ion-paired high-performance-liquid-chromatographic method with solid-phase extraction, which was previously developed and reported by our group (12). The limits of detectability for this assay were as follows: trimethoprim, 25 ng/ml; sulfamethoxazole, 250 ng/ml; and N^4-acetylsulfamethoxazole, 25 ng/ml. The standard curve of the assay was linear over the range of 0.5 to 32 μg/ml for trimethoprim and N^4-acetylsulfamethoxazole and 5 to 320 μg/ml for sulfamethoxazole. The within- and between-day assay coefficients of variation for trimethoprim and N^4-acetylsulfamethoxazole over the range of concentrations from 2 to 16 μg/ml and for sulfamethoxazole over the range of concentrations from 20 to 160 μg/ml were <6% and <9%, respectively.

Data analysis. Pharmacokinetic parameters calculated from steady-state serum drug concentration data were determined by standard noncompartmental procedures (6). The maximum (C_{max}) and minimum (C_{min}) concentrations and the time to achieve the maximum concentration (T_{max}) were obtained by visual inspection of each subject's serum drug concentration-time profiles. The elimination rate constant was estimated by fitting an open one-compartment model with first-order absorption to the observed serum drug concentration-time data by using a weighted (reciprocal squared concentration) nonlinear least-squares regression (PCNONLIN; Statistical Consultants Inc., Lexington, Ky.). The elimination half-life ($t_{1/2}$) was calculated by dividing ln 2 by the elimination rate constant. Area under the serum drug concentration-time curve (AUC) during a steady-state dosing interval was estimated by the linear trapezoidal rule from time zero to 6 h following the last dose. Apparent clearance (CL/F) was calculated by dividing dose by AUC. Renal clearance (CL_R) was the ratio of A_e to AUC, where A_e is the amount of unchanged drug recovered in urine at steady state from 0 to 6 h. Apparent volume of distribution (V/F) was determined from CL/F divided by the elimination rate constant. The fraction of drug excreted unchanged in the urine (f_e) was determined from the ratio of A_e to dose. Data are reported as mean ± standard deviation (SD) unless otherwise noted.

RESULTS

The age and weight of the six subjects in this study were 26.7 ± 3.4 years and 73.7 ± 4.8 kg, respectively. Baseline laboratory values were within normal limits for all subjects. The daily dose of trimethoprim was 12.6 ± 0.6 mg/kg and of sulfamethoxazole was 63.3 ± 2.7 mg/kg.

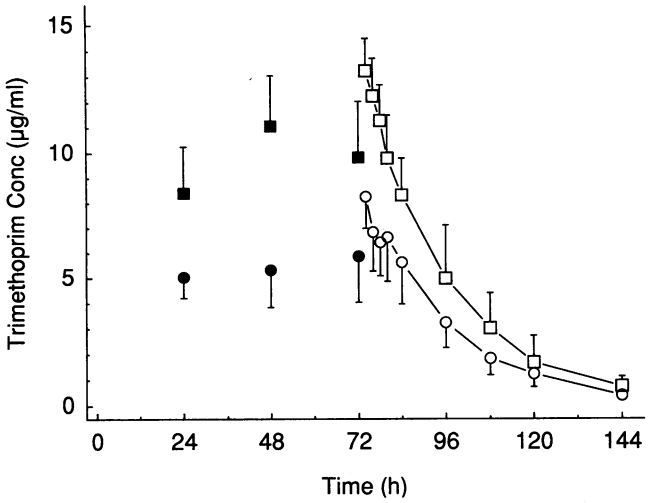

FIG. 1. Mean ± SD serum trimethoprim concentrations. Solid squares and circles are C_{min} values for 20 and 12 mg/kg/day, respectively. Open squares and circles are serum drug concentrations following the last dose for 20 mg/kg/day (n = 7) and 12 mg/kg/day (n = 6), respectively. The daily dose was evenly divided and administered every 6 h.

Plots of the mean steady-state serum drug concentration-time profile after the last dose for trimethoprim and sulfamethoxazole are presented in Fig. 1 and 2, respectively. For visual clarity of the figures, not all early time points are graphed. These plots also show the mean C_{min} values obtained after the 4th, 8th, and 12th doses (i.e., the end of days 1, 2, and 3). Serum drug concentrations from our previous report of 20-mg/kg/day trimethoprim and 100-mg/kg/day sulfamethoxazole are plotted for comparison (20).

Estimates of individual noncompartmental pharmacoki-

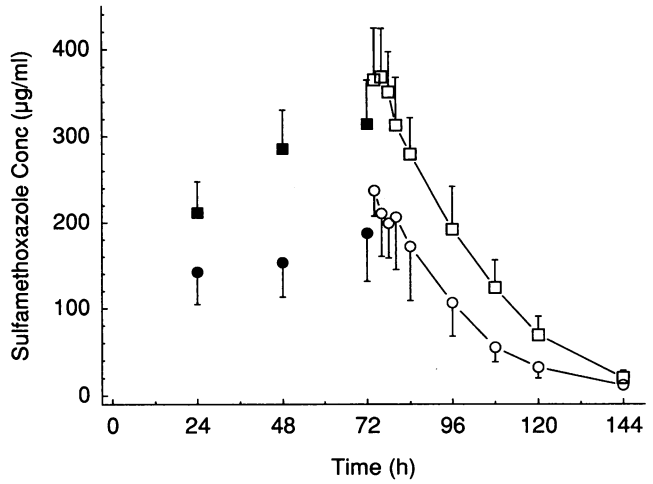

FIG. 2. Mean ± SD serum sulfamethoxazole concentrations. Solid squares and circles are C_{min} values for 100 and 60 mg/kg/day, respectively. Open squares and circles are serum drug concentrations following the last dose for 100 mg/kg/day (n = 7) and 60 mg/kg/day (n = 6), respectively. The daily dose was evenly divided and administered every 6 h.

TABLE 1. Trimethoprim steady-state pharmacokinetic parameters (n = 6)[a]

Subject	Dose (mg/kg/day)	C_{max} (μg/ml)	C_{min} (μg/ml)	T_{max} (h)	AUC (mg · h/liter)	$t_{1/2}$ (h)	V/F (liter/kg)	CL/F (ml/min/kg)	CL_R (ml/min/kg)	f_e (%)
1	12.6	6.0	4.2	1.7	26.1	13.1	2.298	2.019	1.377	68.2
2	12.8	9.5	7.7	2.0	48.5	14.2	1.357	1.104	0.538	48.7
3	12.1	5.5	4.4	2.3	29.4	15.2	2.265	1.721	0.886	51.5
4	13.4	9.4	7.3	0.3	49.2	19.4	1.902	1.132	0.749	66.2
5	13.0	9.0	6.9	1.7	46.6	13.9	1.401	1.165	0.951	81.6
6	11.9	10.4	5.8	1.0	34.9	11.9	1.471	1.424	0.843	59.2
Mean	12.6	8.3	6.1	1.5	39.1	14.6	1.782	1.428	0.891	62.6
SD	0.6	2.0	1.5	0.7	10.3	2.6	0.433	0.373	0.278	12.1

netic parameters for trimethoprim and sulfamethoxazole are listed in Tables 1 and 2, respectively. Parameters of N^4-acetylsulfamethoxazole are C_{max}, 35.3 ± 8.3 μg/ml; C_{min}, 30.1 ± 6.2 μg/ml; T_{max}, 2.5 ± 1.9 h; AUC, 173.1 ± 34.2 mg · h/liter; $t_{1/2}$, 15.6 ± 2.7 h; CL_R, 0.385 ± 0.120 ml/min/kg; and f_e, 20.9% ± 4.5%. Although limitations exist in a nonconcurrent comparison of data from this study with those from our previous investigation (20), similarities in CL/F, V/F, and $t_{1/2}$ between the two doses for the three individual compounds were observed. Furthermore, C_{max}, C_{min}, and AUC were directly proportional to changes in dose. These results indicate that, within the range of the two doses studied, the disposition of trimethoprim, sulfamethoxazole, and N^4-acetylsulfamethoxazole appears to follow a first-order process.

The reduced-dose regimen of trimethoprim-sulfamethoxazole was well tolerated by the subjects. No subject withdrew from the study. This contrasts with our previous report in which 5 of 12 subjects (42%) did not complete the study because of intolerable toxicity (20). The side effects noted by the six subjects in the current report include nausea (n = 4), headache (n = 5), fine tremors (n = 2), and anxiety (n = 1). The nausea was transient and regressed as the subjects continued to take the drug. No hematologic or blood chemistry anomalies were observed when assessed immediately after and 3 days postadministration of the last dose. Comparison of the toxicities in the three subjects who participated in both trials revealed striking differences in tolerability. Subject 1 experienced no adverse effects in this trial but complained of anorexia, nausea, headache, and lethargy and had a twofold increase in serum transaminases (aspartate aminotransferase, alanine aminotransferase) in the earlier study. Subject 2 complained only of a mild headache with the lower dose of co-trimoxazole but had nausea, anorexia, headache, and peripheral tremors with the higher dose. Subject 3 developed nausea, anxiety, headache, and a fine peripheral tremor in this study. In the previous investigation, he had the same adverse effects in addition to a 31% decrease in leukocyte count from baseline.

DISCUSSION

Conventional therapy for PCP with 20-mg/kg trimethoprim and 100-mg/kg sulfamethoxazole daily is widely prescribed for AIDS patients as per the manufacturer's package insert. However, serum drug concentrations achieved with this conventional dose as shown in Fig. 1 and 2 and reported by Lee et al. (13, 14) are in excess (as much as or more than twofold higher) of the proposed therapeutic ranges for PCP. The reduced dose used in this current investigation of healthy subjects was better tolerated than the conventional dose. No subject withdrew from the reduced-dose study because of intolerable side effects. The side effects (nausea, headache, fine tremors, and anxiety) were transient and did not require any therapeutic intervention. No ill effect was observed for blood chemistry or hematologic laboratory values when assessed immediately and 3 days after administration of the last dose. This contrasts with our previous report of conventional-dose trimethoprim-sulfamethoxazole, in which an inverse relationship between a decreased absolute neutrophil count (assessed 3 days postdosing) and systemic drug exposure was established (20).

Sattler et al. demonstrated that maintaining trimethoprim concentrations between 5 to 8 μg/ml decreased drug toxicity without an apparent diminution in efficacy (17). Doses were adjusted to maintain concentrations within the 5- to 8-μg/ml range on the basis of samples collected 0.5 h before the dose and 1.5 h after the completion of the intravenous infusion or ingestion of oral dose (16). In pediatric leukemia patients treated for PCP, peak concentrations (2 h post-oral dose)

TABLE 2. Sulfamethoxazole steady-state pharmacokinetic parameters (n = 6)[a]

Subject	Dose (mg/kg/day)	C_{max} (μg/ml)	C_{min} (μg/ml)	T_{max} (h)	AUC (mg · h/liter)	$t_{1/2}$ (h)	V/F (liter/kg)	CL/F (ml/min/kg)	CL_R (ml/min/kg)	f_e (%)
1	63.2	209	198	1.7	1,042.9	11.3	0.248	0.253	0.013	5.3
2	64.2	245	223	2.0	1,333.5	14.7	0.255	0.201	0.026	13.1
3	60.7	166	134	2.3	876.0	14.1	0.353	0.289	0.018	6.4
4	66.9	269	225	2.3	1,455.5	17.8	0.295	0.191	0.019	10.2
5	65.2	295	229	1.7	1,560.1	15.3	0.231	0.174	0.008	4.6
6	59.7	296	185	1.0	1,039.0	10.7	0.222	0.239	0.041	17.3
Mean	63.3	247	199	1.8	1,217.8	14.0	0.267	0.225	0.021	9.5
SD	2.7	52	36	0.5	270.7	2.6	0.049	0.043	0.012	5.0

ranging from 3 to 5 μg/ml for trimethoprim and 100 to 150 μg/ml for sulfamethoxazole were associated with therapeutic efficacy (9). Fong et al. treated PCP in 101 AIDS patients with 20 mg of trimethoprim per kg and 100 mg of sulfamethoxazole per kg daily (n = 54) versus 15 mg/kg and 75 mg/kg (n = 47), respectively (4). No difference in outcome was observed, but patients in the lower-dose group had less liver transaminase elevation (P = 0.02) and a trend toward less leukopenia (P = 0.06). Preliminary data reported by these same investigators indicate that maintaining peak sulfamethoxazole concentrations below 200 μg/ml may decrease the incidence of leukopenia (3). These reports indicate the feasibility of administering a reduced dose of trimethoprim-sulfamethoxazole for treating PCP in AIDS patients.

The daily dose of 12 mg of trimethoprim per kg and 60 mg of sulfamethoxazole per kg yielded steady-state C_{max} serum trimethoprim concentrations after 72 h of dosing of 8.3 ± 2.0 μg/ml as shown in Fig. 1 and listed individually in Table 1. These steady-state C_{max} trimethoprim values were within or above the therapeutic range of 3 to 5 μg/ml (2 h post-oral dose) or 5 to 8 μg/ml for all subjects. Similar findings with sulfamethoxazole were also observed in that no subject had potentially subtherapeutic concentrations (i.e., <100 μg/ml) during steady-state dosing (Fig. 2 at 74 h and Table 2).

Peak samples were not collected on days 1 through 3; only trough samples were obtained. The mean C_{min} values at the end of day 1 of 12-mg/kg trimethoprim and 60-mg/kg sulfamethoxazole (i.e., C_{min} after four doses) are shown at 24 h in Fig. 1 and 2, respectively. The ranges of the day 1 C_{min} values are 3.8 to 6.2 μg/ml and 89 to 201 μg/ml, respectively. Calculated 2-h-post-oral dose serum drug concentrations within the same dosing interval as these day 1 C_{min} values were 6.1 ± 0.9 μg/ml (range, 4.6 to 7.2 μg/ml) for trimethoprim and 175 ± 48 μg/ml (range, 109 to 257 μg/ml) for sulfamethoxazole. These predicted C_{max} values are within or above the therapeutic range as reported by Hughes et al. (9), but the C_{max} and C_{min} trimethoprim concentrations for one subject (subject 3) were below the 5- to 8-μg/ml range noted by Sattler et al. (17). Similarly, the mean day 2 C_{min} trimethoprim concentration of 5.3 ± 1.5 μg/ml (range, 3.6 to 7.2 μg/ml) shown at 48 h in Fig. 1 and the calculated mean day 2 C_{max} value of 6.4 ± 1.7 μg/ml (range, 4.4 to 8.3 μg/ml) indicate that some subjects (n = 2) were below Sattler's therapeutic range.

As our data indicate and consistent with expectations, one can anticipate that intersubject variability may not uniformly achieve therapeutic drug concentrations in all patients within the proposed ranges after 24 to 48 h of receiving 12-mg/kg trimethoprim and 60-mg/kg sulfamethoxazole. As described above, serum drug concentrations achieved with this dose are acceptable per the report of Hughes et al. (9) but potentially could be subtherapeutic as defined by Sattler (17) in some patients. This is problematic in that not all patients can be presumed to be within the therapeutic range during the first 1 to 2 days of therapy. Therefore, administering a higher dose of trimethoprim-sulfamethoxazole to rapidly attain therapeutic concentrations could be clinically advantageous. This dosing scheme is most applicable in patients with moderate to severe pneumonia (e.g., indications for corticosteroids) for which rapid attainment of therapeutic concentrations may be more exigent.

Three simulated concentration-time profiles showing dosing schemes of 20-mg/kg/day trimethoprim and 100-mg/kg/day sulfamethoxazole, this same dose for the first 24 h followed by a daily regimen of 12 and 60 mg/kg, respectively,

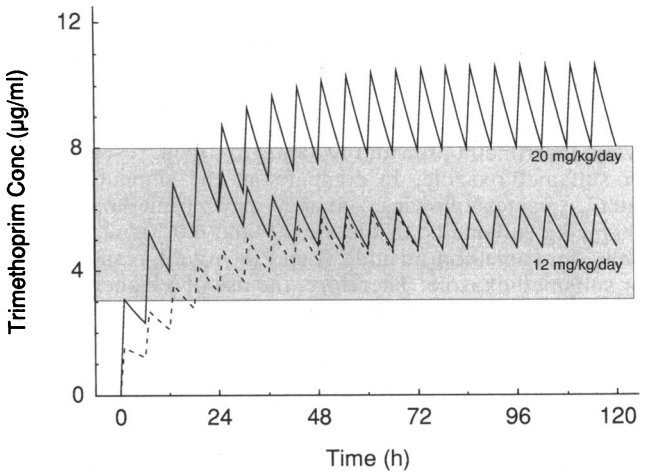

FIG. 3. Simulated serum trimethoprim concentration-time profiles for a 70-kg subject showing three dosing schemes of 20 mg/kg/day, 20 mg/kg/day for the first 24 h followed by 12 mg/kg/day, and only 12 mg/kg/day (dashed line). The daily dose was evenly divided and administered every 6 h. The shaded box shows the proposed therapeutic range of trimethoprim for PCP (9, 17).

and a third plot of the lower dose only are depicted in Fig. 3 and 4. These simulations are based on data from this study and Stevens et al. (20). All dosing regimens were evenly divided and administered every 6 h. Daily trimethoprim doses of 12 and 20 mg/kg produce predicted average steady-state concentrations of 5.6 and 9.5 μg/ml, respectively. The corresponding daily sulfamethoxazole doses of 60 and 100 mg/kg produce predicted average steady-state concentrations of 177 and 298 μg/ml, respectively.

The average calculated half-life of approximately 14 h for trimethoprim and sulfamethoxazole could allow for dosing intervals to be lengthened to every 8 h if desired. Simulations with an 8-h dosing interval were done for 15-mg/kg tri-

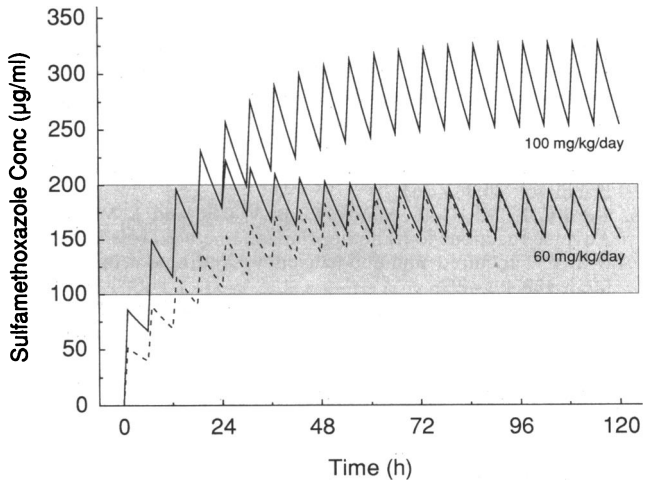

FIG. 4. Simulated serum sulfamethoxazole concentration-time profiles for a 70-kg subject showing three dosing schemes of 100 mg/kg/day, 100 mg/kg/day for the first 24 h followed by 60 mg/kg/day, and only 60 mg/kg/day (dashed line). The daily dose was evenly divided and administered every 6 h. The shaded box shows the proposed therapeutic range of sulfamethoxazole for PCP (3, 9).

methoprim and 75-mg/kg sulfamethoxazole for the first 24 h followed by 12-mg/kg trimethoprim and 60-mg/kg sulfamethoxazole (data not shown). The simulated C_{max} and C_{min} values at the end of 24 h of 15-mg/kg trimethoprim and 75-mg/kg sulfamethoxazole are 5.5 and 3.9 μg/ml, respectively, for trimethoprim and 177 and 125 μg/ml, respectively, for sulfamethoxazole. In comparison, the simulated C_{max} and C_{min} values following 24 h of 20-mg/kg trimethoprim and 100-mg/kg sulfamethoxazole are 7.9 and 6.0 μg/ml, respectively, for trimethoprim and 231 and 180 μg/ml, respectively, for sulfamethoxazole. Therefore, the use of a higher dose of trimethoprim-sulfamethoxazole for the first 24 h of therapy followed by a lower maintenance dose could allow for rapid attainment of therapeutic concentrations while decreasing exposure to potentially excessive drug concentrations. The length of time that trimethoprim or sulfamethoxazole concentrations need to be within certain ranges for either PCP therapy or PCP prophylaxis is uncertain and requires further investigation. For example, trimethoprim-sulfamethoxazole administered thrice weekly was effective for primary and secondary PCP prophylaxis, yet drug concentrations were undetectable in the majority of human immunodeficiency virus-infected patients 48 to 72 h after a dose (19).

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