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Zidovudine, Trimethoprim, and Dapsone Pharmacokinetic Interactions in Patients with Human Immunodeficiency Virus Infection

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Zidovudine is widely prescribed for the treatment of human immunodeficiency virus (HIV) infection. Trimethoprim and dapsone are commonly used in the management of *Pneumocystis carinii* pneumonia in HIV-infected patients. To examine the pharmacokinetic interactions among these drugs, eight HIV-infected patients (26 to 43 years old) with a mean CD4 count of 524.4 ± 405.7 cells per mm^3 received zidovudine (200 mg), trimethoprim (200 mg), and dapsone (100 mg) as single agents and in two- and three-drug combinations. Blood and urine samples were collected at a specified time and analyzed for zidovudine, zidovudine-glucuronide, trimethoprim, dapsone, and monoacetyl-dapsone concentrations under single-dose and steady-state conditions. Zidovudine did not influence the pharmacokinetic disposition of dapsone or trimethoprim. Dapsone had no effect on the pharmacokinetic disposition of zidovudine. Trimethoprim significantly decreased the renal clearance of zidovudine by 58% (5.0 ± 1.8 versus 2.1 ± 0.5 ml/min/kg of body weight [$P < 0.05$]). There was a concurrent 54% decrease in the mean urinary recovery of zidovudine (11.7 ± 3.5 versus 5.4 ± 3.0 [$P < 0.05$]), and the metabolic ratio was decreased by 78% (0.32 ± 0.4 versus 0.07 ± 0.05 [$P < 0.05$]). The mean area under the concentration-time curve from 0 to 6 h of the zidovudine-glucuronide/zidovudine ratio was unchanged. We conclude that zidovudine, trimethoprim, and dapsone can be coadministered to patients with AIDS without significant pharmacokinetic interaction. However, in AIDS patients with liver impairment and impaired glucuronidation, doses of zidovudine may need to be decreased.

The treatment of patients with AIDS often includes therapy with an antiretroviral agent such as zidovudine (ZDV) plus an agent for prophylaxis of *Pneumocystis carinii* pneumonia. Two standard oral therapies for treatment and prophylaxis of *Pneumocystis carinii* pneumonia are trimethoprim (TMP)-sulfamethoxazole and TMP-dapsone (DAP).

Patients with human immunodeficiency virus (HIV) infection have a high incidence of adverse reactions to drugs that are commonly used for the management of AIDS (11, 23). One possible explanation for this high incidence of adverse reactions is the altered pharmacokinetic disposition of drugs in patients with AIDS. Higher levels of TMP and sulfamethoxazole in blood during treatment with standard doses of drugs are seen in patients with AIDS compared with those in other patient populations (3, 28). TMP-sulfamethoxazole treatment can inhibit oxidative metabolism of several drugs, including warfarin, tolbutamide, and phenytoin (12, 16, 34). TMP can also inhibit the renal elimination of digoxin, procainamide, and ZDV (4, 18, 25).

DAP is primarily metabolized in the liver by the cytochrome P-450 mixed-function oxidase and N acetylation mediated by *N*-acetyltransferase (33). Rifampin can decrease the half-life of DAP as a result of enzyme induction, and probenecid can cause a significant reduction in the urinary excretion of DAP (37). We have shown that in AIDS patients with *Pneumocystis carinii* pneumonia, there is a bidirectional interaction between DAP and TMP, in that each will increase the concentration in plasma of the other (20).

ZDV is the most commonly prescribed antiretroviral agent in patients with AIDS. The drug is rapidly absorbed, undergoes hepatic glucuronidation, and is renally excreted as both parent drug (14 to 18% of the oral dose) and ZDV-glucuronide (GZDV) (72 to 75% of the oral dose) (6, 27). It has been shown that probenecid can inhibit the glucuronidation of ZDV, and ZDV can alter the concentrations of phenytoin in serum (7, 17). Since ZDV, TMP, and DAP are commonly coadministered, a better understanding of the interactions between these drugs would allow for modification of dosing regimens to optimize the efficacy and minimize the toxicity of these drugs in the management of AIDS. The objective of this study was to examine the potential pharmacokinetic interactions between these three drugs in patients infected with HIV.

MATERIALS AND METHODS

Patient selection. Eight HIV-infected subjects (seven men) with a mean age of 36.1 ± 6.1 years, mean CD4 cell count of 524.4 ± 405.7 cells per mm^3, and mean weight of 71.8 ± 10.3 kg participated in this randomized, two-treatment-block, three-drug-interaction study. All subjects were nonsmokers and had normal liver and kidney function test results. Subjects were excluded if they had prior hypersensitivity to sulfonamides, sulfones, or TMP or had evidence of glucose-6-phosphate dehydrogenase deficiency. Written informed consent was obtained from each subject, and the study was approved by the Committee on Human Research at the University of California, San Francisco.

Experimental design. This study was an open, crossover study that consisted of two treatment blocks, in which the order of treatment blocks I and II was randomized (Table 1). The first treatment block consisted of 27 days, and the second consisted of 18 days. There was a minimum of a 14-day washout period between each block. All subjects received 200 mg of ZDV (Burroughs Wellcome, Research Triangle Park, N.C.) orally (single-dose study), 200 mg of TMP (Roche Laboratories, Nutley, N.J.) orally every 12 h, and 100 mg of DAP (Jacobus Pharmaceuticals, Princeton, N.J.) orally every 24 h. All drugs were given around the clock, starting at 8 a.m. in the morning. For all blood and urine sample collections, subjects fasted overnight. An intravenous catheter was placed in the forearm vein with a heparin lock to provide a blood sampling site. Serial blood samples were collected in heparinized Vacutainer tubes for ZDV and GZDV at 0, 0.17, 0.33, 0.5, 0.67, 0.83, 1, 2, 3, 4, 5, and 6 h; for TMP at 0, 0.5, 2, 6, 9, 12, 15, and 24 h; and for DAP and monoacetyl-DAP at 0, 2, 4, 6, 9, 12, 24, 48, and 72 h. Urine samples were collected at intervals of 0 to 3 and 3 to 6 h for ZDV.

For treatment block I, on the morning of study day 1, subjects reported to the General Clinical Research Center and received the first dose of ZDV (Table 1).

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TABLE 1. Experimental design[a]

Day	Block I		Block II	
	Treatment	Blood sampling	Treatment	Blood sampling
1	ZDV	Yes	TMP	
2	DAP		TMP	
3	DAP		TMP	
4	DAP		TMP	Yes
5	DAP		TMP	Yes
6	DAP		TMP	
7	DAP		TMP	
8	DAP	Yes	TMP + ZDV	Yes
9		Yes	TMP	
10		Yes	TMP	
11	DAP		TMP + DAP	Yes
12	DAP			Yes
13	DAP			Yes
14	DAP			
15	DAP + ZDV	Yes		
16	DAP		ZDV + DAP + TMP	Yes
17	DAP + TMP	Yes		Yes
18		Yes		Yes
19	DAP + TMP			
20	DAP + TMP			
21	DAP + TMP			
22	DAP + TMP			
23	DAP + TMP			
24	DAP + TMP			
25	DAP + TMP	Yes		
26		Yes		
27		Yes		

[a] Drugs were given at the following doses: ZDV, 200 mg; DAP, 100 mg; TMP, 200 mg.

Blood and urine samples were collected for measurement of ZDV and GZDV concentrations. On study day 2, the subjects received the first dose of DAP. They were observed for 3 h to ensure tolerance of the drug and were discharged with a 6-day supply of DAP. Subjects were asked to keep an accurate record of medication and adverse reactions. On the morning of study day 8, after the subjects had received a dose of DAP, blood samples were obtained for measurement of DAP and monoacetyl-DAP concentrations. Subjects were discharged after the initial 24-h blood sample collection, and the 48- and 72-h samples were obtained by venipuncture. On study day 11, subjects resumed taking DAP. On study day 15, while still taking DAP, subjects received one dose of ZDV, and then blood and urine samples were obtained for measurement of ZDV concentrations. On the morning of study day 17, while subjects continued to take DAP, a dose of TMP was given. Blood samples were obtained for measurement of TMP concentrations. After the 24-h collection period, the subjects were discharged with a 7-day supply of TMP and DAP. On day 25 after subjects had received both TMP and DAP together for 7 days, blood samples were obtained for measurement of TMP, DAP, and monoacetyl-DAP concentrations. The subjects were discharged at the end of study day 27.

After a minimum 14-day washout period, on study day 1 of treatment block II, subjects reported to the General Clinical Research Center to receive TMP. The subjects were observed for 3 h to ensure their tolerance of the drug and were discharged with a 3-day supply of TMP. On the morning of study day 4, after the subjects had received a dose of TMP, blood samples were collected for measurement of TMP concentrations. On study days 5 to 7, the subjects continued to take TMP. On the morning of study day 8, while still taking TMP, the subjects received one dose of ZDV. Blood and urine samples were collected for measurement of ZDV concentrations. On study day 11, after the subjects had received a dose of TMP and DAP, blood samples were obtained for measurement of DAP and monoacetyl-DAP concentrations. On the morning of study day 16, subjects received one dose of all three drugs. Blood samples were obtained for measurement of ZDV, TMP, and DAP concentrations, and urine samples were obtained for measurement of ZDV concentrations. The subjects were discharged at the end of study day 18.

Adverse effects were recorded daily by the subjects, and laboratory data, including complete blood count with differential and platelet count, electrolytes, blood urea nitrogen, creatinine, total protein, albumin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and methemoglobin, were monitored every 5 to 7 days.

Analytical methods. All samples were collected in heparinized Vacutainer tubes, placed immediately on ice, and centrifuged. Plasma was harvested, stored in glass dram vials, and frozen at −20°C to await further processing. Plasma samples were analyzed for ZDV and GZDV by a high-performance liquid chromatography (HPLC) method, as previously published (10). The lower limits of quantitation for this assay were 26.7 ng/ml (0.1 μM) for ZDV and 99 ng/ml (0.21 μM) for GZDV. Interday and intraday coefficients of variation ranged from 0.6 to 5.7% for ZDV to 0.6 to 14.8% for GZDV. Prior to analysis, samples of ZDV in plasma were heat deactivated for 45 min at 56°C to ensure inactivation of the HIV.

TMP, DAP, and monoacetyl-DAP concentrations in plasma were measured by HPLC by the method of Spreux-Varoquaux et al. as previously described (20, 30) and modified as follows. Plasma aliquots were extracted with chloroform-ethyl acetate (3/1). After the lower phase was evaporated, the residue was reconstituted in methylene chloride-methanol-isopropylamine-water (600/39/1/1 [mobile phase]). The normal-phase isocratic HPLC was performed with a Lichrosorb silica column at a flow rate of 1 ml/min and detection at 280 nm. A Hewlett-Packard 1090 HPLC system equipped with a Chem Station 300 was the instrument used. The retention times for TMP, DAP, monoacetyl-DAP, and the internal standard (dinitrobenzyl pyridine) were 4.3, 2.1, 3.4, and 1.2 min, respectively. The lower limit of detection of the method for TMP was 0.5 μg/ml. The interday and intraday coefficients of variation for 0.5 μg/ml were 7.1 and 4.5%, respectively. The lower limit of detection of the method for both DAP and monoacetyl-DAP was 0.1 μg/ml. The interday and intraday coefficients of variation for 0.1 μg/ml were 6.3 and 2.1% for DAP and 5.0 and 3.2% for monoacetyl-DAP, respectively.

Pharmacokinetic calculations. Plasma concentration-versus-time data were analyzed by noncompartmental methods. The maximum concentration (C_{max}) and time of maximum concentration (T_{max}) were determined by visual inspection of the data. The predicted C_{max} at steady state (ssC_{max}) from the single-dose kinetic data was calculated by the equation $ssC_{max} = F \times dose/V(1 - e^{-K_{el}T})$, Where F is the bioavailability, V is the volume of distribution, K_{el} is the elimination rate constant, and T is the dosing interval for DAP and TMP. The values of F were obtained from the literature: for DAP, $F = 93\% \pm 8\%$, and for TMP, $F = 100\%$ (2). Elimination half-lives ($t_{1/2}$) and K_{el} were computed from the terminal slope by best-fit least-squares linear regression of the log concentration-time curve. The area under the plasma concentration-time curve (AUC) was computed by the linear trapezoidal method from 0 to time z of the last measurable sample and extrapolated to infinity for the single-dose condition. The dosing interval (12 h for TMP and 24 h for DAP) was used to calculate the AUC under steady-state conditions (AUC_{ss}). Apparent total body clearance (CL/F) was computed as CL/F = dose/AUC. The renal clearance (CL_R) values of ZDV and GZDV were determined as the ratio of the amount recovered in urine to that of the respective AUC. The urinary recovery (UR) of ZDV was based on the cumulative amounts excreted within the 6-h collection period and was expressed as a percentage of the ZDV dose administered: % UR of zidovudine = 100% × amount/dose. The metabolic ratio was calculated up to 6 h as the amount of ZDV excreted in the urine divided by the amount of GZDV.

Statistical analysis. An analysis of variance for repeated measures was used for comparison of the pharmacokinetic parameters of ZDV, GZDV, TMP, DAP, and monoacetyl-DAP alone or in combination and under steady-state or single-dose conditions. Specific comparisons were made by using the Tukey post hoc test. Differences were considered statistically significant at $P \leq 0.05$. The results are expressed as means ± standard deviations.

RESULTS

A total of eight subjects were enrolled. Two subjects did not complete treatment block II because of a rash with fever that developed after they had received TMP. Therefore, eight subjects completed treatment block I, and six subjects completed treatment block II. All subjects were compliant with the study medication. Subjects were not allowed to receive any medication during the study period other than the study medication and acetaminophen.

ZDV pharmacokinetics. TMP tended to increase the AUC (1.11 ± 0.16 versus 1.46 ± 0.72 μg · h/ml), decrease the CL/F (41.0 ± 3.3 versus 36.2 ± 12.2 ml/min/kg), and significantly decrease the CL_R of ZDV (5.0 ± 1.8 versus 2.1 ± 0.5 ml/min/kg [$P < 0.05$]) (Table 2 and Fig. 1). UR of ZDV decreased by 54% during concurrent TMP treatment (11.7 ± 3.5 versus 5.4 ± 3.0 [$P < 0.05$]), and the metabolic ratio was decreased by 78% (0.32 ± 0.4 versus 0.07 ± 0.05 [$P < 0.05$]). The AUC from 0 to 6 h (AUC_{0-6}) ratio of GZDV to ZDV was unchanged. DAP had no effect on the pharmacokinetic disposition of ZDV (Table 2). Likewise, the combination effect of TMP plus DAP on the pharmacokinetic parameters of ZDV was similar to the effect of TMP alone (Table 2).

TABLE 2. Pharmacokinetic parameters of ZDV and GZDV after administration of 200 mg of ZDV with and without DAP and TMP

Parameter (unit)	Condition[a]			
	ZDV_1 ($n = 8$)	$ZDV_1 + DAP_{ss}$ ($n = 8$)	$ZDV_1 + TMP_{ss}$ ($n = 6$)	$ZDV_1 + TMP_1 + DAP_1$ ($n = 6$)
ZDV				
C_{max} (μg/ml)	1.09 ± 0.54	0.91 ± 0.53	0.93 ± 0.3	1.21 ± 0.57
T_{max} (h)	0.75 ± 0.43	1.1 ± 0.62	1.15 ± 1.08	0.9 ± 0.45
AUC (μg · h/ml)	1.11 ± 0.16	1.12 ± 0.21	1.46 ± 0.72	1.65 ± 1.17
$t_{1/2}$ (h)	1.01 ± 0.10	0.98 ± 0.21	0.93 ± 0.16	0.92 ± 0.36
CL/F (ml/min/kg)	41.0 ± 3.3	41.5 ± 9.2	36.2 ± 12.2	35.0 ± 14.8
CL_R (ml/min/kg)	5.0 ± 1.8[b]	4.6 ± 2.42	2.1 ± 0.5[b]	1.5 ± 0.4[b]
% UR_{0-6}[c]	11.7 ± 3.5[b]	9.8 ± 5.1	5.4 ± 3.0[b]	5.0 ± 4.8[b]
GZDV				
C_{max} (μg/ml)	5.6 ± 1.7	5.2 ± 1.5	5.05 ± 1.03	4.86 ± 1.19
AUC (μg · h/ml)	7.9 ± 0.84	7.67 ± 0.54	7.6 ± 0.68	8.17 ± 1.6
CL_R (ml/min/kg)	5.8 ± 3.7	5.5 ± 3.1	5.9 ± 2.6	5.3 ± 2.8
AUC_{GZDV}/AUC_{ZDV}	6.9 ± 1.3	7.5 ± 2.1	6.2 ± 2.5	7.9 ± 4.5
Metabolic ratio	0.32 ± 0.4[b]	0.16 ± 0.16[b]	0.07 ± 0.05[b]	0.14 ± 0.2[b]

[a] Subscript 1 indicates single dose. Subscript ss indicates steady state. Values are means ± standard deviations.
[b] $P < 0.05$ compared with ZDV alone.
[c] % UR_{0-6}, percentage UR from 0 to 6 h.

TMP pharmacokinetics. The steady-state pharmacokinetic parameters of TMP were not significantly altered by DAP (Table 3). As expected, there was a significant difference in the C_{max} and clearance of TMP between steady-state and single-dose conditions. The ssC_{max} of TMP was 59% higher than the C_{max} achieved with a single dose (3.87 ± 1.98 versus 1.60 ± 0.56 μg/ml [$P < 0.05$]). The predicted ssC_{max} calculated with the single-dose kinetic data was not different from the observed ssC_{max} (3.87 ± 1.98 versus 3.86 ± 1.2 μg/ml). In addition, the clearance of TMP at steady state was 29% lower (1.54 ± 0.86 versus 2.16 ± 0.6 ml/min/kg [$P < 0.05$]) and the AUC_{ss} was 39% higher (39.2 ± 21.0 versus 23.8 ± 9.1 μg · h/ml) than those for the single-dose conditions (Table 3 and Fig. 2). The addition of ZDV to DAP did not alter the pharmacokinetic disposition of TMP (Table 3).

DAP pharmacokinetics. The steady-state pharmacokinetic parameters of DAP were not significantly altered by TMP (Table 4). As expected, similar to TMP for DAP there was a significant difference in the C_{max} and clearance between steady-state and single-dose conditions. The ssC_{max} was 24% higher than the C_{max} under single-dose conditions (2.4 ± 0.81 versus 1.83 ± 0.79 μg/ml [$P < 0.05$]). There was no difference between the predicted ssC_{max} from single-dose kinetic data and the observed ssC_{max} (2.31 ± 1.32 versus 2.4 ± 0.81 μg/ml). The clearance of DAP at steady state was 32% lower (0.54 ± 0.25 versus 0.79 ± 0.49 ml/min/kg [$P < 0.05$]) and the AUC_{ss} was 31% higher (54.8 ± 31.6 versus 37.8 ± 22.5 μg · h/ml) than those under single-dose conditions (Table 4 and Fig. 3). Similarly, the addition of ZDV to TMP did not alter the pharmacokinetic disposition of DAP (Table 4).

Pharmacokinetic parameters for monoacetyl-DAP are shown in Table 4. To assess the acetylation status of these subjects, an acetylator with a monoacetyl-DAP/DAP ratio of <0.35 was defined as a slow acetylator and one with a monoacetyl-DAP/DAP ratio of >0.35 was defined as a fast acetylator (8). There were three slow and five fast acetylators.

DISCUSSION

The pharmacokinetic parameters for ZDV (5, 6, 7, 27, 29), TMP (13, 15, 24, 31, 32, 36), and DAP (1, 2, 8, 22, 37) at baseline found in our study in asymptomatic subjects with HIV infection are in agreement with previously published data for healthy volunteers and HIV-seropositive patients.

In this study, we found that TMP tended to increase the AUC and to significantly decrease the CL_R of ZDV by 58%. Concurrently, there was a significant decrease in the UR of ZDV and the metabolic ratio of ZDV to GZDV, with no change in the AUC ratio of ZDV to GZDV. The decrease in the CL_R of ZDV is consistent with the report by Chatton et al. (4), who found a 48% decrease in the CL_R of ZDV after TMP administration.

A likely mechanism for the decrease in the CL_R of ZDV is that TMP competes for the renal secretion of ZDV at the renal tubular site. TMP is transported by the organic cation system, and it has also been shown to inhibit the renal excretion of drugs such as procainamide and digoxin that are also transported by the same system (18, 25).

As expected, there was a significant difference in the C_{max} achieved between steady-state and single-dose conditions for both TMP and DAP. For TMP, the ssC_{max} was 59% higher and

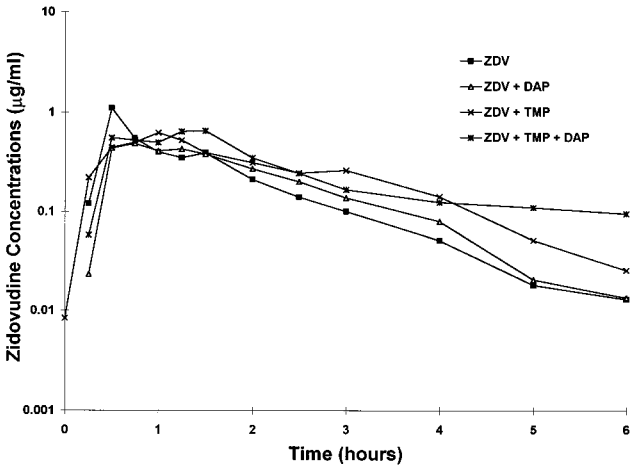

FIG. 1. Comparison of plasma drug concentration-time profiles obtained for subjects with HIV infection under single-dose conditions with ZDV alone or in combination with DAP and TMP.

TABLE 3. Pharmacokinetic parameters of TMP after administration of 200 mg of TMP with and without DAP and ZDV

Parameter (unit)	Condition[a]			
	TMP_{ss} ($n = 6$)	$TMP_{ss} + DAP_{ss}$ ($n = 8$)	$TMP_1 + DAP_1$ ($n = 8$)	$TMP_1 + DAP_1 + ZDV_1$ ($n = 6$)
C_{max} (μg/ml)	4.32 ± 1.71	3.87 ± 1.98[b]	1.60 ± 0.56[b]	1.82 ± 0.42
T_{max} (h)	1.17 ± 0.68	2.58 ± 1.50	2.75 ± 1.17	1.92 ± 0.80
AUC (μg · h/ml)	33.1 ± 10.8	39.2 ± 21.0	23.8 ± 9.1	23.4 ± 8.2
$t_{1/2}$ (h)	10.9 ± 2.2	8.9 ± 3.5	9.9 ± 2.4	8.7 ± 2.1
CL/F (ml/min/kg)	1.58 ± 0.63	1.54 ± 0.86[b]	2.16 ± 0.6[b]	2.18 ± 0.6

[a] Subscript 1 indicates single dose. Subscript ss indicates steady state. Values are means ± standard deviations.
[b] $P < 0.05$ for steady state versus single-dose conditions.

the clearance was 29% lower than those under single-dose conditions. Steady-state levels of TMP achieved in blood in adults in 2 to 3 days with a standard dose regimen have been reported to be about 50% higher than those achieved after a single dose (36). In addition, progressive accumulation of TMP has been described for patients treated with high doses of TMP (20 mg/kg/day)-sulfamethoxazole for *Pneumocystis carinii* pneumonia (14, 35).

Similarly, with DAP, the ssC_{max} was 31% higher and the clearance was 46% lower than those under single-dose conditions. It has been reported for other patient populations that the steady-state concentrations after daily administration of DAP are about twice as high as those resulting from a single dose (37). That the clearance of DAP decreased under steady-state conditions suggests that there might be a change in either the oxidative metabolism or acetylation of DAP. Acetylation status in our subjects remained stable over time and was not associated with changes in the clearance of DAP. Therefore, it is possible that there is a decrease in the oxidative metabolism of DAP under steady-state conditions. It has been shown that the oxidative metabolism of DAP accounts for >90% of the variability in the CL/F of DAP (22).

When we used the single-dose kinetic data to predict the ssC_{max} of TMP and DAP, we found that there was no difference between the observed C_{max} and the predicted C_{max}. However, since we found and others have similarly reported (36, 37) that clearance of TMP and DAP decreased after chronic administration, we suspect that this finding of no difference between the predicted C_{max} and observed C_{max} may be a failure to truly detect a difference. Since C_{max} is also a function of bioavailability, V, and the absorption rate constant, the variability of these parameters may obscure the ability to truly detect a difference in C_{max}.

Our previous study suggested that there might be a bidirectional interaction between TMP and DAP by which each drug elevated the concentration in plasma of the other (20). However, in our current study of eight subjects, we found no apparent interaction between TMP and DAP. Several explanations could account for the disparity in these results. (i) The number of subjects studied may be inadequate to detect a significant difference. (ii) The previous study compared the concentrations of TMP and DAP from two separate clinical trials. (iii) The subjects in our current study, primarily asymptomatic HIV infected, differed from the AIDS patients (treated for *Pneumocystis carinii* pneumonia) who were in the previous trials.

Because two subjects were excluded from the study as a result of a rash that developed after TMP treatment, data for TMP were available only for six subjects. In our previous study, there were 22 patients in the TMP-DAP group, 10 in the DAP-alone group, and 11 in the TMP-sulfamethoxazole group.

In our previous study, we measured the concentrations of TMP and DAP as part of an open study of DAP and a randomized study of TMP-DAP or TMP-sulfamethoxazole in treating *Pneumocystis carinii* pneumonia in patients with AIDS. Because we compared the concentrations of TMP and DAP from two separate trials, the patients did not serve as their own

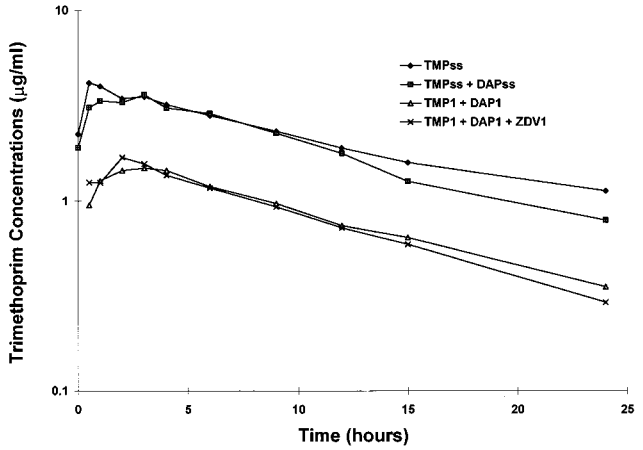

FIG. 2. Comparison of plasma drug concentration-time profiles obtained for subjects with HIV infection under steady-state (ss) and single-dose (TMP1, DAP1, and ZDV1) conditions with TMP alone or in combination with DAP and ZDV.

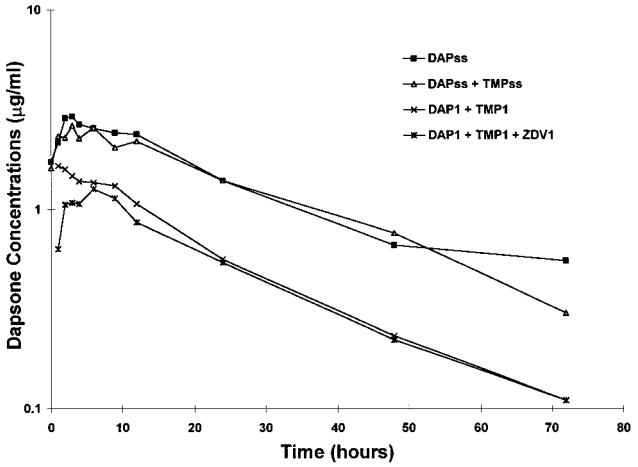

FIG. 3. Comparison of plasma drug concentration-time profiles obtained for subjects with HIV infection under steady-state (ss) and single-dose (DAP1, TMP1, and ZDV1) conditions with DAP alone or in combination with TMP and ZDV.

TABLE 4. Pharmacokinetic parameters of DAP and monoacetyl-DAP after administration of 100 mg of DAP with and without TMP and ZDV

Parameter (unit)	Condition[a]			
	DAP_{ss} ($n = 8$)	$DAP_{ss} + TMP_{ss}$ ($n = 8$)	$DAP_1 + TMP_1$ ($n = 6$)	$DAP_1 + TMP_1 + ZDV_1$ ($n = 6$)
DAP				
C_{max} (μg/ml)	2.5 ± 0.65	2.4 ± 0.81[b]	1.83 ± 0.79[b]	1.42 ± 0.63
T_{max} (h)	2.0 ± 0.89	3.17 ± 1.17	2.67 ± 1.47	4.0 ± 3.1
AUC (μg · h/ml)	49.6 ± 28.6	54.8 ± 31.6	37.8 ± 22.5	36.5 ± 16.4
$t_{1/2}$ (h)	21.2 ± 7.8	27.4 ± 14.9	17.2 ± 2.4	17.8 ± 5.1
CL/F (ml/min/kg)	0.59 ± 0.27	0.54 ± 0.25[b]	0.79 ± 0.49[b]	0.70 ± 0.20
Monoacetyl-DAP				
C_{max} (μg/ml)	1.14 ± 0.50	1.15 ± 0.24	1.07 ± 0.79	0.72 ± 0.32
AUC (μg · h/ml)	20.9 ± 17.6	19.1 ± 3.4	22.9 ± 13.7	16.2 ± 5.8

[a] Subscript 1 indicates single dose. Subscript ss indicates steady state. Values are means ± standard deviations.
[b] $P < 0.05$ for steady-state versus single-dose conditions.

controls. Therefore, the differences observed may be a result of the interindividual variability that occurs, especially in severely ill patients.

The more likely explanation for the findings in our current study is that the subjects studied differed from those studied previously. The subjects that participated in the current study were HIV seropositive; however, they were asymptomatic and were not receiving any prophylactic agents for opportunistic infections or treatment for an acute illness. In our previous study, all patients had an AIDS diagnosis and were hospitalized for the treatment of *Pneumocystis carinii* pneumonia. Therefore, there may be a difference in the metabolism of these drugs in these two groups of patients. We have found that AIDS patients with acute illnesses have altered patterns of drug metabolism compared with those of HIV-infected patients without an acute illness (21). Specifically, AIDS patients with acute illnesses have an increased prevalence of slow acetylation (93%) compared with that in HIV-infected patients without an acute illness (58%). In this study, only three of the eight subjects (38%) were slow acetylators. In addition, a difference in the level of tumor necrosis factor found between HIV-infected patients without AIDS and patients with AIDS may be an explanation for the difference in the metabolism of these drugs. It has been shown that tumor necrosis factor can cause marked depression of levels of cytochrome P-450 and other drug-metabolizing enzymes in the liver and many organs (9). In patients with AIDS, the circulating levels of tumor necrosis factor are higher than those in patients who are HIV infected without AIDS (19, 26).

Finally, that there is an increased incidence of rash and other adverse effects to TMP-sulfamethoxazole therapy in HIV-infected patients has been well described (3, 11, 23, 28). Since the objective of this study was not to treat patients with *Pneumocystis carinii* pneumonia, we gave a lower dose of TMP (200 mg twice daily) than that normally required for treatment. However, despite its lower dose, TMP still caused a rash with fever in two of the eight subjects (25%) we studied. It has been suggested that TMP is well tolerated and that the adverse effects induced by TMP-sulfamethoxazole treatment are due to the sulfa component of the combination therapy (25). In contrast, our study showed that TMP alone can also cause a significant rash, which required the subjects to discontinue the study.

In summary, ZDV had no effect on the pharmacokinetic disposition of TMP and DAP. DAP did not influence the pharmacokinetic disposition of ZDV. However, TMP appears to decrease the CL_R of ZDV. Since only 20% of the CL/F of ZDV is accounted for by CL_R, we conclude that ZDV, TMP, and DAP can be coadministered in patients with AIDS without significant pharmacokinetic interaction. However, in AIDS patients with liver impairment and impaired glucuronidation who are receiving ZDV and TMP, doses of ZDV may need to be decreased.

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