ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 1996, p. 230–233 Vol. 40, No. 1
0066-4804/96/$04.00+0
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# Absence of Effect of Trimethoprim-Sulfamethoxazole on Pharmacokinetics of Zidovudine in Patients Infected with Human Immunodeficiency Virus

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Received 14 December 1994/Returned for modification 13 May 1995/Accepted 15 October 1995

**Pharmacokinetic parameters of zidovudine (ZDV) were not altered in 16 patients receiving concomitant therapy with ZDV and trimethoprim-sulfamethoxazole by oral administration. ZDV areas under the concentration-time curves were (means ± standard deviations) 1.80 ± 0.70 and 1.69 ± 0.64 μg · h/ml in the absence and presence of trimethoprim-sulfamethoxazole, respectively. ZDV clearances were 1.57 ± 0.61 and 1.74 ± 0.66 liters/h/kg, respectively.**

Zidovudine (ZDV) is a selective inhibitor of reverse transcriptase of the human immunodeficiency virus (HIV) (11, 27). Although ZDV has been widely studied (2, 8, 9, 13–15, 19, 20, 26, 28), several issues related to its pharmacokinetics remain to be analyzed. Among the issues with greater clinical relevance is the possible interaction of ZDV with other drugs usually prescribed in combination with it (4). Trimethoprim-sulfamethoxazole (TMP-SMX), a drug regarded to be the most efficient for the chemoprophylaxis of *Pneumocystis carinii* pneumonia (PCP) in patients with HIV infection (5, 10, 18), stands out because of its wide use. From a pharmacokinetic viewpoint, ZDV and TMP-SMX use the same hepatic glucuronidation route. Thus, theoretically, the elimination of one or both agents may be altered when they are administered together. At present, data from in vitro (17, 23, 25) and in vivo (7, 16, 21) studies suggest that the interaction of the drugs lacks clinical relevance. Nevertheless, no studies have evaluated the possible interactions occurring when both drugs are administered orally, as happens in clinical practice. The aim of the present study is to investigate the possible influence of the concomitant use of TMP-SMX, as primary chemoprophylaxis of PCP, on ZDV pharmacokinetics when both drugs are orally administered.

We selected 16 HIV-infected patients who fulfilled the following criteria: 18 to 60 years of age, treatment with oral ZDV (250 mg every 12 h) over a minimum of 15 days, indication of primary prophylaxis of PCP ($CD4^+$ lymphocyte count of $<200/\mu l$ or $<20\%$ of the total lymphocyte count), and clinical stability with a normal hydration state. The patients gave their informed consent to participate in the study.

We excluded from the study patients who had shown a previous intolerance to TMP-SMX or sulfonamides or who were currently using intravenous drugs as well as those who had received treatment other than ZDV 15 days prior to the start of the study. Patients who had a serum creatinine concentration of >1.2 mg/dl, alteration of the hepatic function, diarrhea or known disorders of the intestinal absorption, or severe opportunistic infections at the time of study were also excluded.

On day 1 of the study (phase 1) patients received 250 mg of ZDV orally with 100 ml of water after 8 h of nocturnal fasting. Blood samples (5 ml) were drawn immediately before and at 0.5, 1, 1.5, 2, 3, 4, and 6 h after ZDV administration. The following day the patients began prophylaxis of PCP with TMP-SMX (160/800 mg orally twice a day, three times per week). They continued with an oral dosage of 250 mg of ZDV every 12 h. Between the subsequent 15 and 60 days we performed the second phase of the study. Patients received 250 mg of ZDV plus 160/800 mg of TMP-SMX orally with 100 ml of water after 8 h of nocturnal fasting. Blood samples (five ml) were drawn immediately before and at 0.5, 1, 1.5, 2, 3, 4, and 6 h after administration of the drugs. The interval between the two pharmacokinetic studies ranged between 17 and 37 days with a mean of 25 ± 6.6 days.

Samples were immediately subjected to centrifugation and maintained at −70°C until we analyzed the concentrations in plasma. ZDV and glucuronide of ZDV (G-ZDV) concentrations in plasma were assessed by double-antibody radioimmunoassay (ZDV-Trac; INCSTAR Co., Stillwater, Minn.) with prior digestion with β-D-glucuronidase for the quantitation of

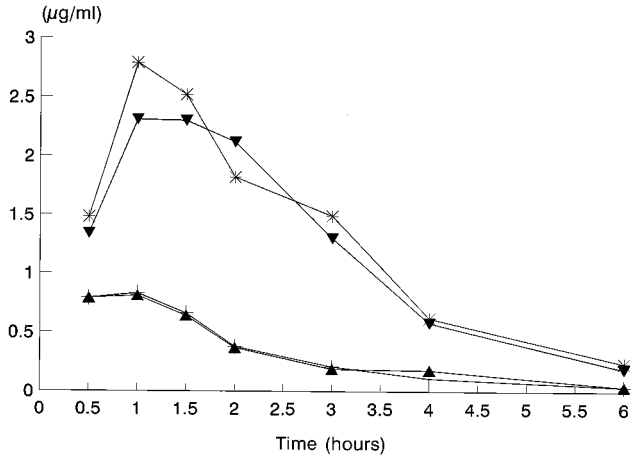


FIG. 1. Mean plasma concentration curves of ZDV and G-ZDV after the administration of ZDV alone (+ and ∗, respectively) and in combination with TMP-SMX (▲ and ▼, respectively).

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TABLE 1. Characteristics of patients

| Patient | Age (yr) | Sex[a] | Risk factor[b] | CDC/93 classification[c] | No. of $CD4^+$ lymphocytes/μl | Length of treatment | |
|---|---|---|---|---|---|---|---|
| | | | | | | ZDV (mo) | TMP-SMX (days) |
| 1 | 31 | M | HOMO | B3 | 97 | 12 | 37 |
| 2 | 45 | M | HOMO | A3 | 197 | 16 | 35 |
| 3 | 31 | M | IVDU | A3 | 122 | 0.5 | 17 |
| 4 | 28 | M | IVDU | A3 | 12 | 6 | 24 |
| 5 | 30 | F | IVDU | A3 | 198 | 14 | 19 |
| 6 | 35 | M | IVDU | A3 | 78 | 9 | 19 |
| 7 | 36 | M | HETE | B3 | 185 | 20 | 19 |
| 8 | 33 | M | IVDU | C3 | 128 | 30 | 19 |
| 9 | 31 | F | IVDU | A3 | 114 | 1 | 27 |
| 10 | 32 | M | IVDU | B3 | 161 | 11 | 24 |
| 11 | 22 | M | IVDU | A3 | 198 | 2 | 20 |
| 12 | 28 | M | IVDU | B3 | 190 | 1 | 31 |
| 13 | 33 | F | HETE | B3 | 176 | 3 | 18 |
| 14 | 25 | M | IVDU | B3 | 164 | 10 | 29 |
| 15 | 30 | M | IVDU | B3 | 180 | 24 | 32 |
| 16 | 34 | M | IVDU | C3 | 100 | 1 | 30 |
| Mean ± SD | 32 ± 5 | | | | 143 ± 54 | 10 ± 9 | 25 ± 6.6 |

[a] M, male; F, female.
[b] HOMO, male homosexual contact; IVDU, intravenous drug use; HETE, heterosexual contact.
[c] Classification of HIV infection by Centers for Disease Control and Prevention 1993 revised system (6).

G-ZDV. The concentration range for the assay was from 4.3 to 6,795 ng/ml. The sensitivity of the method was 0.3 ng/ml. For a concentration of 500 ng/ml, the intra-assay variability was 8.8% and the interassay variability was 10.28% (coefficient of variation). The cross-reactivity of the method with TMP and SMX is lower than 0.001% and with G-ZDV is 0.0031% (22).

$C_{max}$ was defined as the peak concentration in plasma obtained after drug administration, and $T_{max}$ was defined as the time to reach $C_{max}$. A noncompartmental pharmacokinetic analysis was used. The serum ZDV and G-ZDV concentration-versus-time profiles were analyzed by linear least-squares regression with the program PKCALC (24). The terminal elimination phase was identified by visual inspection of each patient plot, and the elimination rate constant was estimated as the slope of the best-fit regression line of the terminal elimination phase. Terminal half-life ($t_{1/2}$) was calculated as 0.693 divided by the elimination rate constant. Area under the concentration-time curve (AUC) was calculated by the linear trapezoidal rule and then extrapolated to infinity. The total body clearance (CL) was calculated as dose/AUC. As ZDV was given orally, CL and the volume of distribution at steady state ($V_{ss}$) are expressed as CL/$F$ and $V_{ss}/F$ (where $F$ is a bioavailability factor of 65% [2]). The results are reported as means ± standard deviations (SD).

The sample size of 16 patients was selected on the basis that it was sufficient to detect a difference between means equal to 0.8 SD at $P = 0.05$ (two-sided) with a power of 90%. The statistical significance was determined with the Wilcoxon signed rank test. Association between continuous variables was determined by linear correlation (Pearson's coefficient). A $P$ value of $<0.05$ was considered significant.

The characteristics of the 16 patients are summarized in Table 1. The weights of the patients on the first day of the study were between 48 and 87 kg (mean weight, 67.1 ± 11.6 kg). On the first day of the second phase, weights ranged from 49 to 86 kg (mean weight, 66.5 ± 10.4 kg). ZDV doses according to body weight were 3.85 ± 0.67 mg/kg (range, 2.87 to 5) and 3.84 ± 0.62 mg/kg (range, 2.9 to 5) in phases 1 and 2, respectively.

Figure 1 shows the mean plasma concentration curves of ZDV and G-ZDV after the administration of ZDV alone and in combination with TMP-SMX. Mean $C_{max}$ were 1.21 ± 0.71 and 1.12 ± 0.61 μg/ml for ZDV alone and in combination with TMP-SMX, respectively (ranges, 0.22 to 2.39 and 0.34 to 2.71 μg/ml). The $T_{max}$, $t_{1/2}$, AUC, CL/$F$, and $V_{ss}/F$ for ZDV are summarized in Table 2. Mean $C_{max}$ were 3.33 ± 1.74 and 3.17 ± 1.95 μg/ml for G-ZDV alone and in combination with TMP-SMX, respectively (ranges, 1.16 to 7 and 0.89 to 6.95 μg/ml). $T_{max}$, $t_{1/2}$, and AUC for G-ZDV are summarized in Table 3. Finally, mean $AUC_{G\text{-}ZDV}/AUC_{ZDV}$ coefficients were 4.16 ± 3.34 and 4.22 ± 4.16 in phases 1 and 2, respectively.

None of the pharmacokinetic parameters of ZDV and G-ZDV studied revealed statistical differences related to the coadministration of TMP-SMX (Tables 2 and 3). A power analysis was made, resulting in a power of 84% to detect a 20% difference in mean CL of ZDV. We did not find any association between the ZDV doses measured in milligrams per kilogram and the $C_{max}$ of ZDV when ZDV was administered

TABLE 2. Pharmacokinetic parameters of ZDV[a]

| Phase of study | $C_{max}$ (μg/ml) | $T_{max}$ (h) | AUC (μg · h/ml) | CL/$F$ (liters/h/kg) | $V_{ss}/F$ (liters/kg) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|
| ZDV | 1.21 ± 0.71 | 1.18 ± 0.79 | 1.80 ± 0.70 | 1.57 ± 0.61 | 4.10 ± 2.55 | 1.61 ± 1.32 |
| ZDV + TMP-SMX | 1.12 ± 0.61 | 0.96 ± 0.42 | 1.69 ± 0.64 | 1.74 ± 0.66 | 3.98 ± 2.12 | 1.44 ± 0.42 |

[a] Results are means ± SD. Differences between phase 1 and phase 2 values were not significant.

TABLE 3. Pharmacokinetic parameters of G-ZDV[a]

| Phase of study | $C_{max}$ (μg/ml) | $T_{max}$ (h) | AUC (μg · h/ml) | $t_{1/2}$ (h) | $AUC_{G\text{-}ZDV}/AUC_{ZDV}$ |
|---|---|---|---|---|---|
| ZDV | 3.33 ± 1.74 | 1.56 ± 0.89 | 6.96 ± 5.48 | 1.38 ± 0.49 | 4.16 ± 3.34 |
| ZDV + TMP-SMX | 3.17 ± 1.95 | 1.28 ± 0.51 | 6.61 ± 6.35 | 1.20 ± 0.51 | 4.22 ± 4.16 |

[a] Results are means ± SD. Differences between phase 1 and phase 2 values were not significant.

alone ($r = 0.14$) or in combination with TMP-SMX ($r = -0.16$).

Our results corroborate those of previous reports (7, 16, 21) in the sense that the concomitant oral administration of TMP-SMX does not significantly alter the clearance of ZDV. Concentrations of ZDV and of its main metabolite in plasma decrease simultaneously both in the presence and in the absence of TMP-SMX. Finally, the $AUC_{G\text{-}ZDV}/AUC_{ZDV}$ coefficients were not altered with the coadministration of TMP-SMX and ZDV.

Pazin et al. (21) did not find significant differences between the pharmacokinetic parameters of ZDV alone and those of ZDV given intravenously in combination with oral TMP-SMX. Chatton et al. (7) found that the successive oral administration of TMP-SMX and TMP to HIV-infected patients who had received ZDV by intravenous perfusion did not significantly alter the total clearance or distribution of ZDV in such patients. Nevertheless, they found a significant decrease in the renal clearance of ZDV and G-ZDV and in the metabolic ratio in the presence of TMP-SMX and TMP. These authors suggest that TMP increases the extrarenal elimination of ZDV, probably by biliary excretion, and/or inhibits the tubular secretion of ZDV and G-ZDV. Lee et al. (16) also found that the concomitant administration of TMP decreases the renal clearance of ZDV significantly. The design of our study did not include the analysis of the ZDV and G-ZDV concentrations in urine, so we could not study interaction at the level of renal elimination. However, given that this is not the main route for the elimination of ZDV (2), this interaction would have clinical importance only in those situations in which glucuronidation would be limited by a hepatic disease or inhibited by other drugs.

From a theoretical viewpoint, the interaction of drugs with ZDV may occur at different levels of pharmacokinetic activity, e.g., absorption, metabolism, activation to ZDV triphosphate, or elimination (4). In the case of TMP-SMX, the most probable mechanism is at the level of hepatic glucuronidation. Seventy-five percent of the initial oral dose of ZDV is metabolized to G-ZDV by the action of UDPglucuronosyltransferase in the hepatic microsome (12). SMX and TMP are metabolized partially by means of hepatic glucuronidation (1, 3), so an enzymatic interaction during formation of G-ZDV would be expected (28). Nevertheless, experimental in vitro assays performed with human hepatic microsomes suggest that sulfonamides, including SMX, are only weak inhibitors of UDPglucuronosyltransferase (17, 23, 25). The results in the present paper and those previously published (7, 16, 21) corroborate the findings of the in vitro studies.

We conclude that there is no significant clinical interaction between the administration of 160/800 mg of TMP-SMX and the pharmacokinetics of ZDV in patients infected with HIV when both drugs are administered orally.

This work was supported in part by a grant from the Consejeria de Salud de la Junta de Andalucia, Spain.

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