Pharmacokinetic interaction between zidovudine and trimethoprim/sulphamethoxazole in HIV-1 infected children

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OBJECTIVE: To evaluate the effect of the antimicrobial agent trimethoprim/sulphamethoxazole (TMP/SMX) on the pharmacokinetic properties of the antiretroviral drug zidovudine (ZDV).
DESIGN: This single dose, open label, crossover study involved the oral administration of ZDV (150 mg/m^2) alone and in combination with oral TMP/SMX (2.5 mg/kg) on two separate occasions. Serial blood samples (0 to 8 h) were collected, and concentrations of ZDV and its glucuronide metabolite were quantified using a radioimmunoassay. ZDV pharmacokinetics were determined by noncompartmental analysis.
PATIENTS AND SETTING: Six HIV-1 infected children aged four months to five years were recruited from the HIV clinic at The Hospital for Sick Children, Toronto, Ontario. Only three patients completed both study phases and were included in the pharmacokinetic analysis.
MAIN RESULTS: With TMP/SMX therapy, no statistically significant changes were observed in ZDV pharmacokinetic parameters. However, there was a trend towards increased ZDV half-life and area under the concentration versus time curve, as well as decreased apparent oral clearance. Similarly, a trend towards an increased half-life of the ZDV-glucuronide metabolite was also observed.
CONCLUSION: The changes in ZDV pharmacokinetics in the presence of TMP/SMX did not reach statistical significance, most likely due to the limited number of patients involved. Despite the limited data, a possible interaction between ZDV and TMP/SMX in young HIV-1 infected children should be considered, and patients may require close clinical monitoring.

Key Words: *Children; Drug interactions; HIV; Trimethoprim/sulphamethoxazole; Zidovudine*

Interaction pharmacocinétique entre la zidovudine et le triméthoprime-sulfaméthoxazole chez les enfants infectés par le VIH-1

OBJECTIF : Évaluer l'effet de l'agent antimicrobien triméthoprime-sulfaméthoxazole (TMP-SMX) sur les caractéristiques pharmacocinétiques du médicament antirétroviral zidovudine (ZDV).
MODÈLE : Cette étude croisée, ouverte, à dose unique impliquait l'administration orale de ZDV (150 mg/m^2) seul et en combinaison avec du TMP-SMX (2,5 mg/kg) à deux occasions différentes. Des échantillons de sang sériés (0 à 8 h) ont été recueillis et des concentrations de ZDV et de son glucurométabolite ont été quantifiées par radio-immuno-dosage. La pharmacocinétique de la ZDV a été déterminée au moyen d'une analyse non compartimentale.
PATIENTS ET CONTEXTE : Six enfants âgés de quatre mois à cinq ans et infectés par le VIH-1 ont été recrutés par le biais

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de la clinique du VIH du *Hospital for Sick Children*, à Toronto, en Ontario. Seuls trois patients ont terminé les deux phases de l'étude et ont été inclus dans l'analyse sur la pharmacocinétique.

PRINCIPAUX RÉSULTATS : Avec le TMP-SMX, aucun changement significatif n'a été observé dans les paramètres de la pharmacocinétique de la ZDV. Cependant, on a observé une tendance vers une augmentation de la demi-vie de la ZDV et de l'aire sous la courbe de concentration par rapport à la courbe de temps, de même qu'une diminution de la clairance orale visible. De même, on a également observé une tendance vers une augmentation de la demi-vie du glucurométabolite de la ZDV.

CONCLUSION : Les changements dans la pharmacocinétique de la ZDV en présence de TMP-SMX n'ont pas atteint une signification statistique, ce qui est probablement dû au nombre limité de patients étudiés. Malgré l'insuffisance des données, il faut songer à une possible interaction entre la ZDV et le TMP-SMX chez les jeunes enfants infectés par le VIH-1, et par conséquent, une surveillance clinique rigoureuse peut s'avérer nécessaire chez ces patients.

Medical management of HIV-1 infected children involves the use of multiple drug therapies. A commonly prescribed drug combination is the reverse transcriptase inhibitor, zidovudine (ZDV), and the antimicrobial agent, trimethoprim/sulphamethoxazole (TMP/SMX) (1). ZDV, the first antiviral drug to be approved for treatment of HIV, remains a cornerstone in many AIDS drug regimens. TMP/SMX is the preferred agent for both the treatment and prophylaxis of *pneumocystis carinii* (PCP). Both ZDV and TMP/SMX are known to induce hematological side effects in AIDS patients that often result in dosage adjustments or discontinuation of the drugs. As a consequence of often being prescribed together and sharing similar toxicological profiles, potential drug-drug interactions between these two drugs are of extreme clinical importance.

Following oral administration in humans, ZDV is rapidly absorbed; however, a significant first-pass effect results in an average bioavailability of only 65% (2,3). Metabolism of ZDV results in the formation of an ether glucuronide (GZDV), the primary metabolite, and two minor metabolites, 3 -amino-3 -deoxythymidine (AMT) and AMT glucuronide. Approximately 60% to 70% of the parent drug is recovered in the urine as GZDV. AMT, the metabolite that is hypothesized to be responsible for ZDV-associated hematological side effects, is formed through the action of the cytochrome P-450 reductase enzyme system (4). Conversely, the main metabolite of SMX is an *N*-acetyl derivative, which represents 60% to 65% of an SMX dose, whereas TMP does not undergo metabolism to any appreciable extent. Based on their different pathways of biotransformation, we would not expect ZDV and TMP/SMX to interact at the metabolic level, and indeed, this has been demonstrated by numerous investigators, both in vivo and in vitro (5-8).

Although metabolism of ZDV is its major route of elimination, 17% to 30% of the drug is excreted in the urine as the unchanged parent drug (2,3,9). Studies have indicated that although ZDV is a weak organic anion, the presence of an azido group and a high pKa (9.68) may confer organic cation properties to the agent, making it zwitterionic in nature. As a result, multiple membrane transporters appear to be involved in the renal tubular secretion of ZDV. This type of cross-reactivity with respect to both organic anion and organic cation transporters in the kidney has been demonstrated with other zwitterionic compounds including the cephalosporins, cephaloridine and cefadroxil (10,11). TMP is an organic cation known to undergo renal tubular secretion through the organic cation system (12), whereas SMX, an organic anion, is eliminated via the organic anion system (13). Therefore, ZDV and TMP/SMX may interact at the level of the kidney through competition for similar renal tubular transport systems.

This interaction was demonstrated in adults by Chatton et al (5) and Lee et al (7), who observed that the apparent oral clearance (Cl_o) of ZDV decreased by 12% and the renal clearance (Cl_r) decreased by 59% in the presence of TMP/SMX. The authors concluded that this interaction would only be clinically important in cases where the metabolism of ZDV was impaired, for example in patients who had severe hepatic dysfunction. Another patient population that has a lowered capacity for drug metabolism is children under five years of age who have underdeveloped metabolic capabilities (14). Thus, the goal of the present study was to examine the possible pharmacokinetic drug-drug interaction between ZDV and TMP/SMX in HIV-1 infected children under the age of five years.

PATIENTS AND METHODS

Study population: Six HIV-1 infected children aged four months to five years (mean 2.7 years) who were receiving ZDV and TMP/SMX therapy were recruited from the outpatient HIV clinic at The Hospital for Sick Children, Toronto, Ontario. A physical examination was performed at the start of the study. All of the study patients were clinically stable at study entry. The study was approved by the Ethics Committee at The Hospital for Sick Children. Before participating in the study, parents and/or guardians gave their written informed consent for their children to participate. Patients who were intolerant to either ZDV or TMP/SMX or who had abnormal liver or kidney function tests were excluded from the study.

Study design: The study used a single dose, open label, crossover design involving two phases. During phase A, patients received 150 mg/m^2 oral ZDV alone (Retrovir Syrup, Glaxo Wellcome Inc, Mississauga, Ontario), and during phase B, 150 mg/m^2 of oral ZDV (Retrovir Syrup, Glaxo Wellcome Inc) was administered in combination with 2.5 mg/kg oral TMP/SMX (Septra Pediatric Suspension, Glaxo Wellcome Inc). Before each study day, concurrent medications used by the patients were withheld for a period of five to seven half-lives to ensure that these agents did not interfere with the study medications. Normal dosing of ZDV (phase A) or ZDV and TMP/SMX (phase B) was continued throughout the study. On both study days, the same procedure was followed. Patients arrived at the hospital in the morning having not eaten for at least 1 h. A peripheral

indwelling intravenous line was started in the forearm vein, and one blood sample was drawn into an unheparinized vacutainer (Becton-Dickinson, USA). Patients were then administered the appropriate study medications. Further blood samples were drawn at 0.5, 1, 2, 3, 4, 6 and 8 h. Immediately following blood collection, the samples were centrifuged at 1000×*g,* and the serum was collected and stored at –20°C until analysis. Patients did not eat or drink for at least 1 h after the administration of the study medications.

Laboratory analysis: ZDV and GZDV were quantified in patient serum samples using a commercially available radioimmunoassay kit (ZDV-Trac, INCSTAR Co, USA). Simultaneous determination of ZDV and GZDV was accomplished using the modified radioimmunoassay methodology of Tadepalli et al (15). The lower limit of detection of ZDV and GZDV was 2.42 ng/mL and 6.82 ng/mL, respectively, and the interassay variability was 4.9% (16). The cross reactivity of the method was less than 0.03% for TMP and SMX (16), and 0.003% for GZDV (17).

Pharmacokinetic analysis: ZDV and GZDV pharmacokinetic parameters were determined by noncompartmental analysis using the nonlinear, least squares regression program WINNONLIN, version 1.0 (Scientific Consultants Inc, USA). The terminal elimination rate constant (K_{el}) for each patient was determined using the least squares regression of individual patient's logarithmic concentration versus time plots. Four to six data points were included in each calculation of K_{el}. The apparent half-life was then calculated as $0.693/K_{el}$. Values for the areas under the concentration time curves (AUC_{0-}) were calculated using the linear trapezoidal method, and the Cl_o was determined as dose/AUC_{0-}.

Statistical analysis: Differences in pharmacokinetic parameters of ZDV and GZDV in the presence and absence of TMP/SMX, were evaluated by the nonparametric Wilcoxon signed rank test (Sigma Stat 2.03, SPSS Inc, USA). Differences were considered statistically significant at $P<0.05$.

RESULTS

The study initially recruited five male patients and one female patient. Their ages at study entry ranged from four months to four years, seven months, with a mean of two years, six months. The patients weighed 5.8 kg to 17.4 kg (mean 13.2 kg) and were 60 cm to 103 cm in height (mean 85.3 cm). Their T4 cell counts ranged from 280 to 1646 (mean 824). The patients had been receiving ZDV for a mean time of 20 months (range zero to 42 months) and TMP/SMX for 19 months (range one to 39 months). HIV infection was acquired through perinatal transmission in all six patients. Two patients were receiving ketoconazole for oropharyngeal candidiasis (thrush), and one patient received fluconazole for thrush. One patient also received cantharone for molluscum contagiosum and podophyllin for perianal warts. All patients were receiving lamivudine (3TC) in addition to ZDV and TMP/SMX.

Three of the six patients recruited completed both phases A and B (two males, one female). Two patients (both male) completed only one study phase; the parents of one patient withdrew consent, and the second patient was changed from a regimen of 3TC and ZDV to stavudine (d4T) and a protease inhibitor, and was no longer eligible for the study. A third male patient did not complete phase A or B of the study as a result of his parent withdrawing consent during the first study phase. Therefore, only the three patients who completed both study phases were included in the pharmacokinetic analysis. Although none of the results reached statistical significance, there was a trend towards a decrease in the mean Cl_o of ZDV, and a trend towards an increase in mean ZDV AUC_{0-} and half-life in the presence of TMP/SMX. The mean Cl_o of ZDV decreased by 33% and the mean AUC_{0-} and half-life of ZDV increased by 40% and 16%, respectively. The mean AUC_{0-} of GZDV decreased by 12% and the mean half-life increased by 40%. Table 1 summarizes mean ZDV and GZDV pharmacokinetic parameters within the study subjects.

TABLE 1
Mean pharmacokinetic parameters of zidovudine (ZDV) and zidovudine glucuronide (GZDV) in the presence and absence of trimethoprim/sulphamethoxazole (TMP/SMX)

Parameter	Treatment day	
	ZDV alone (n=3)	ZDV + TMP/SMX (n=5)
ZDV		
AUC_{0-} (ng/min/L)	142.6±61.1	246.7±162.3
Cl_o (mL/min)	989.2±261.8	739.4±390.0
$T_{1/2}$ (min)	55.0±15.5	70.1±24.2
GZDV		
AUC_{0-} (ng/min/L)	761.2±293.3	914.3±390.8
$T_{1/2}$ (min)	55.4±3.1	77.5±31.5

AUC Area under the concentration versus time curve; Cl_o Apparent oral clearance; $T_{1/2}$ Plasma half-life

The Cl_o of ZDV in the female patient decreased by 37% and was accompanied by increases of 73% and 114% in ZDV AUC_{0-} and half-life, respectively. The youngest patient to complete the study experienced decreases of 51% and 22% in ZDV Cl_o and half-life, respectively. As a result, the AUC_{0-} of ZDV increased by 85%. The pharmacokinetics of the oldest patient remained largely unaffected in the presence of TMP/SMX therapy.

DISCUSSION

A high incidence of adverse drug reactions has been reported in paediatric HIV-1 infected patients receiving the antiviral drug ZDV and the antimicrobial TMP/SMX concurrently (18). Nevertheless, TMP/SMX is often prescribed to HIV-1 positive patients treated with ZDV because it remains the preferred agent for the prophylaxis and treatment of PCP (18).

It was our hypothesis that an interaction between TMP/SMX and ZDV could occur at the level of renal tubular secretion through competition for similar renal membrane transporters. In contrast with adult patients, we expected that this interaction would likely result in a clinically significant alteration in ZDV Cl_o in young children due to the immaturity of the metabolic pathways (13). As a result, Cl_r pathways of drugs that are highly metabolized by the liver become an increasingly impor-

tant route for overall drug elimination in young children, further contributing to the possibility of renal drug-drug interactions.

The pharmacokinetics of ZDV and GZDV observed in our patients during the oral administration of ZDV were comparable with those reported previously in HIV-1 infected children, although these studies involved extremely large patient age ranges (19-21). The AUC_{0-} of GZDV was five times higher than AUC_{0-} of ZDV (761.2 versus 142.7 ng/min/L) and showed large interpatient variability, which is consistent with previous studies in both HIV-1 infected adults and children (22,23). Our study, although limited in its sample size, is the first to characterize the kinetics of both ZDV and GZDV in toddlers and infants under the age of five years.

Trends observed during the co-administration of TMP/SMX in the present study included a tendency towards a decreased Cl_o, as well as higher AUC_{0-} values and longer ZDV and GZDV half-lives. We would not expect the changes in ZDV and GZDV kinetics to be related to altered ZDV glucuronidation, but rather solely due to a change in the renal tubular secretion of both ZDV and GZDV by TMP/SMX because previous studies have reported that ZDV metabolism is unaltered in the presence of TMP/SMX (5,8,22). For example, in human liver microsomes, TMP/SMX was only a weak inhibitor of glucuronidation, even at high concentrations (8,24). Alternatively, several studies have demonstrated that the renal tubular transport of ZDV is inhibited by both organic cations and organic anions. In our laboratory, the renal tubular transport of ZDV was inhibited by the organic cations cimetidine, quinine, quinidine and TMP in a continuous renal epithelial cell line grown as a monolayer on a permeable surface (25). These results corroborate the work of Aiba et al (26) who reported that the cationic compounds cimetidine and imipramine, and the anionic compound probenecid alter the renal secretion of ZDV in rats. Similarly, TMP/SMX has been shown to interact with the renal elimination of the nucleoside analog 3TC in both humans and animal models (27,28).

The largest change in ZDV Cl_o was observed in the youngest patient who completed the study, a male one-and-a-half-years old. In the presence of TMP/SMX therapy, his ZDV AUC_{0-} increased by 85% and Cl_o was decreased by 51%. As expected, the smallest observed change in ZDV pharmacokinetics was seen in the oldest patient participating, a five-year-old male. At age five years, we would expect glucuronidation capabilities to be mature, hence any interaction that occurs would be very small and similar to that which has been observed in adult patients. Interestingly, the second oldest patient, a four-and-a-half-year-old female, experienced a substantial change in ZDV pharmacokinetics in the presence of TMP/SMX cotherapy. Previous studies in adults have demonstrated that the Cl_r of ZDV accounts for a greater percentage of total ZDV clearance in women compared with men (29). Thus, although this patient presumably had fully developed glucuronidation pathways, the percentage of ZDV eliminated by the kidney may have been increased, contributing to the renal drug-drug interaction observed. Because this study was limited in size, these interactions need to be confirmed in a larger cohort of patients.

Originally, 12 HIV-1 infected children were to be involved in this study. This number was generated by a standard sample size calculation (30). We assumed a change of 35% in pharmacokinetic parameters such as Cl_o with a power of detection of 80% would be clinically significant. Following the conclusion of the study, a power analysis was performed on each of the pharmacokinetic parameters according to Rosner (31). According to these equations, the power for detecting a difference in the pharmacokinetics of ZDV and GZDV in our study in the presence and absence of TMP/SMX therapy was less than 40%. This low power is a reflection of the small number of patients involved in the study. Problems in finding patients for this study can be attributed to a number of factors. First and foremost, management of HIV patients changes rapidly and dramatically. As a result, guidelines for treatment of HIV and AIDS have changed considerably in the past few years and standard therapy now involves the use of combination therapies. Particularly, combinations of two reverse transcriptase inhibitors and a protease inhibitor (eg, 3TC, ZDV and saquinavir), and the combination of d4T and a protease inhibitor are quite common. ZDV use as monotherapy is becoming uncommon, due in part to viral resistance and changing attitudes towards the treatment of HIV. As a result, having patients withhold doses of concurrently used antiretrovirals, such as the protease inhibitors, for the purpose of participating in a study introduces serious ethical concerns, as well as a number of practical considerations. With this realization in mind, the intent of the present study was not to provide a predictive model for determining the extent to which drugs within a multidrug regimen will interact at the renal level, but rather to demonstrate the importance of renal drug-drug interactions by the use of one uncomplicated example.

CONCLUSION

Although our results did not reach statistical significance, there was a trend towards an increase in ZDV half-life and AUC_{0-}, and a decrease in Cl_o in the presence of TMP/SMX. Considering the dose dependant side effects of both ZDV and TMP/SMX, concurrent administration of these two agents should be closely monitored in HIV-1 infected paediatric patients under the age of five years. Clinical monitoring should include routine biochemical monitoring as well as clinical monitoring of hematological side effects such as anemia (complete blood count and differential). Should severe adverse effects be observed, dosage adjustments or discontinuation of one or both of the drugs may be necessary.

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