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Trimethoprim, alone or in combination with sulphamethoxazole, decreases the renal excretion of zidovudine and its glucuronide

J. Y. CHATTON[1], A. MUNAFO, J. P. CHAVE, F. STEINHÄUSLIN, F. ROCH-RAMEL[1], M. P. GLAUSER & J. BIOLLAZ

Département de Médecine interne, Centre Hospitalier Universitaire Vaudois and [1]Institut de Pharmacologie et de Toxicologie de l'Université de Lausanne, Switzerland

Trimethoprim and trimethoprim-sulphamethoxazole (co-trimoxazole) are often prescribed in HIV patients treated with zidovudine. The pharmacokinetics of zidovudine, after a dose of 3 mg kg^{-1} by constant rate intravenous infusion over 1 h were evaluated in nine HIV patients in an open, randomized, three-phase crossover study, without and with trimethoprim (150 mg) and trimethoprim-sulphamethoxazole (160 and 800 mg). The metabolic clearance of zidovudine was not significantly influenced by trimethoprim-sulphamethoxazole and trimethoprim. However, the renal clearance of zidovudine was decreased by 58 and 48%, respectively, and that of its glucuronide by 27 and 20% ($P < 0.05$). The fraction of the dose excreted as the parent compound fell by 47 and 39% and the metabolic ratio by 48 and 43% ($P < 0.05$). This kinetic drug interaction, apparently due solely to trimethoprim, may only be clinically important when hepatic glucuronidation is also impaired by liver disease or inhibited by other drugs.

Keywords zidovudine pharmacokinetics drug interactions trimethoprim co-trimoxazole

Introduction

Zidovudine (Z), an inhibitor of reverse transcriptase, is a widely used drug for the treatment of AIDS (Yarchoan *et al.*, 1989). Its main route of elimination (~ 75%) is by metabolism to a glucuronide (ZG). The rest undergoes renal excretion (Blum *et al.*, 1988). Probenecid, an organic anion inhibitor, decreases the renal clearance of zidovudine in AIDS patients (de Miranda *et al.*, 1989), suggesting that zidovudine is secreted by the organic anion transport system (Blum *et al.*, 1988). Conversely it has been suggested that, since it is a weak base, it is secreted by the organic cation transport system (Henry *et al.*, 1988; Kornhauser *et al.*, 1989).

Trimethoprim, either alone or in combination with sulphamethoxazole, is often prescribed to AIDS patients for the treatment of opportunistic infections. Trimethoprim, an organic base, undergoes oxidative metabolism and conjugation in the liver. The drug and its metabolites are excreted by glomerular filtration and tubular secretion (Cacini, 1987). Sulphamethoxazole is mostly acetylated in the liver, and parent drug and metabolites are excreted in the urine (Bach *et al.*, 1973).

Therefore, a potential for kinetic interaction between zidovudine and trimethoprim exists at the level of both glucuronidation and renal secretion. This dual inhibition could have clinical relevance, as shown for probenecid (Kornhauser *et al.*, 1989; Mays *et al.*, 1991). The aim of our study was to investigate the influence of concomitant administration of trimethoprim or trimethoprim-sulphamethoxazole on the metabolism and the renal excretion of zidovudine.

Methods

Subjects and study design

Nine HIV-infected patients (six males, three females) receiving zidovudine (10 mg kg^{-1} day^{-1}) were recruited at the outpatient AIDS clinic of the Division of Infectious Diseases of the Hospital. They were 25–41 years old (median 31) weighed 44–91 kg (median 61), and had normal cardiac and renal function (creatinine clearance 65–116 ml min^{-1} 1.73 m^{-2}, median 105). HIV infection was acquired through i.v. drug abuse in six, homosexual relations in two and heterosexual relations in one patient.

Correspondence: Dr J. Biollaz, Division de Pharmacologie clinique, Département de Médecine interne, CHUV, CH-1011 Lausanne, Switzerland

Only patients with liver function test results < 3 times the upper normal values were enrolled into the study. One patient had had hepatitis C and four hepatitis B (two chronic). All patients had a CDC/WHO stage IV HIV infection (four IVC1, three IVC2, one IVB, one IVA+B). The median CD4 lymphocyte count was 269 μl^{-1} (range 54–577). No patient received any known inhibitor or inducer of metabolism as concurrent medication. Three of the i.v. drug abusers were receiving methadone, four patients were taking flunitrazepam and one patient oxazepam. The patients gave their written informed consent to participate in the study, which was approved by the Hospital Ethics Committee. This open, cross-over, randomized study had three phases, each separated by a 1 week wash-out period. The subjects were on a diet of their own choice. In phase A, the patients received at 08.00 h (approximately 10 h after the last oral dose) 3 mg kg^{-1} zidovudine (Retrovir®, Wellcome) as a 1 h i.v. infusion. In phase B, they received in addition 160 mg trimethoprim and 800 mg sulphamethoxazole orally (Bactrim®, Hoffman-La-Roche). In phase C, they received Z plus 150 mg trimethoprim orally (Monotrim® 100 mg, Rorer, 1.5 tablets). Adequate urine flow was maintained by the ingestion of 150 ml mineral water per hour. In each phase, 3 ml blood samples were drawn before the start of the infusion, and at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7 and 8 h after the end of the infusion. The serum was separated by centrifugation and kept frozen at −20° C until analyzed. Urine was collected from 0 to 3 h, 3 to 5 h, 5 to 7 h and 7 to 9 h from the start of the infusion; its pH was measured and aliquots were frozen.

Analytical methods

Zidovudine and its glucuronide metabolite (ZG) were measured in serum and urine by h.p.l.c. according to the method of Good *et al.* (1988). The mobile phase consisted of 25 mM ammonium phosphate pH 2.2/acetonitrile (85:15) and the flow rate was 1 ml min^{-1}. For Z and ZG, the assay limits were ≤ 0.04 μM and ≤ 0.02 μM and the interday coefficients of variation were 1.5% and 2.4%, respectively.

Pharmacokinetic calculations

The concentrations were expressed in molar units, based on molecular weights of 267.24 for Z and 443.37 for ZG. The terminal elimination rate constant λ_z, of Z was estimated by weighted (1/observed^2) non-linear regression having fitted the data with a two-compartment open model with intravenous infusion. The terminal half-life ($t_{½,z}$) was calculated from $\ln 2/\lambda_z$. AUC values were estimated by the log-trapezoidal method; the area under the first moment curve (AUMC) was calculated by the linear trapezoidal rule; both areas were extrapolated to infinity. Clearance (CL) was calculated from dose/AUC, and renal clearance (CL_R) from the amount excreted in 9 h divided by the AUC up to 9 h; non-renal clearance (CL_{NR}) was obtained by difference. The mean residence time (MRT) was calculated from AUMC/AUC − T/2, where T is the duration of the infusion. The volumes of distribution were calculated, in the terminal phase (V_z) as CL/λ_z, and at steady state (V_{ss}) as CL·MRT. Finally, the metabolic ratio was calculated up to 9 h as the amount of Z excreted in the urine divided by that of ZG.

Statistical analysis

An analysis of variance (ANOVA) for repeated measures was used for the comparison of the pharmacokinetic parameters of Z and ZG between the three study phases. When a significant treatment effect was detected, differences were subjected to a Least-Significant-Difference test. The significance level was set at 0.05. Unless stated otherwise, the results are expressed as mean ± s.e. mean.

Results

The mean plasma concentrations of zidovudine and its glucuronide are shown in Figure 1 for the three study phases. The profiles varied only slightly in the presence of either trimethoprim alone or in combination with sulphamethoxazole. However, urinary excretion was altered with renal clearance being decreased in phases B and C *vs* phase A by means of 58% and 48%, respect-

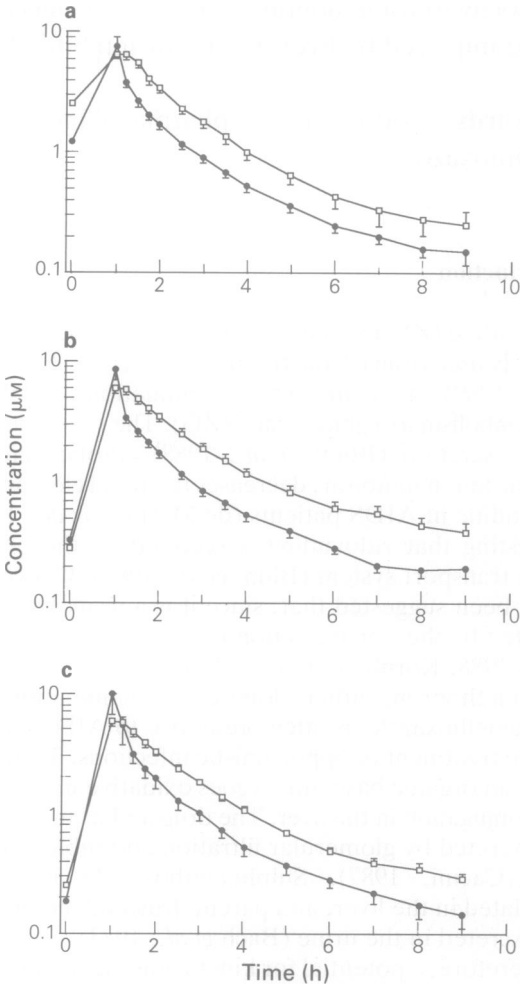

Figure 1 Mean (± s.e. mean) serum concentrations of zidovudine (•) and its glucuronide (□): (a) zidovudine alone; (b) zidovudine plus trimethoprim-sulphamethoxazole; (c) zidovudine plus trimethoprim.

Table 1 Pharmacokinetic parameters describing the disposition of zidovudine (Z) and its glucuronide (ZG) (mean ± s.e. mean). (A: Z alone; B: Z + T-S; C: Z + T)

		A	*B*	*C*
Z				
AUC	(μM h)	9.5 ± 0.7	11.2 ± 1.3	12.4 ± 2.7
CL	($l\,h^{-1}\,kg^{-1}$)	1.22 ± 0.12	1.08 ± 0.09	1.07 ± 0.11
$t_{½,z}$	(h)	1.8 ± 0.2	1.7 ± 0.1	1.9 ± 0.1
V_z	($l\,kg^{-1}$)	3.1 ± 0.4	2.5 ± 0.2	3.0 ± 0.3
V_{ss}	($l\,kg^{-1}$)	2.5 ± 0.3	2.0 ± 0.2	2.1 ± 0.2
MRT	(h)	2.0 ± 0.1	1.8 ± 0.1	1.9 ± 0.2
% dose		24 ± 3	13 ± 2*	15 ± 3*
CL_R	($l\,h^{-1}\,kg^{-1}$)	0.34 ± 0.05	0.14 ± 0.03*	0.17 ± 0.03*
CL_{NR}	($l\,h^{-1}\,kg^{-1}$)	0.89 ± 0.11	0.91 ± 0.09	0.90 ± 0.10
ZG				
AUC	(μM h)	13.6 ± 1.5	16.3 ± 1.6	15.0 ± 0.8
% dose		70 ± 3	63 ± 7	70 ± 5
CL_R	($l\,h^{-1}\,kg^{-1}$)	0.70 ± 0.07	0.51 ± 0.07*	0.56 ± 0.04*
Z/ZG				
AUC ratio		0.80 ± 0.12	0.72 ± 0.08	0.86 ± 0.20
Metabolic ratio		0.36 ± 0.06	0.19 ± 0.02*	0.21 ± 0.04*

*Significantly different from phase A ($P \leq 0.05$, LSD).

ively for Z, and 27% and 20% for ZG (Table 1). The fraction of the dose excreted as the parent compound was also decreased (by 47% and 39%, respectively), as was the metabolic ratio (48% and 43%). The other pharmacokinetic parameters were not statistically different between the three phases. According to the study design and the observed residual variance, a difference in the systemic clearance of more than 30% can be excluded at an α level of 0.05 and a β level of 0.2. None of the parameters was different between phases B and C.

Discussion

Net clearance, metabolic clearance and distribution of Z, were not altered significantly by the administration of trimethoprim and trimethoprim-sulphamethoxazole. This corroborates the preliminary findings of Pazin *et al.* (1990). However, the renal clearance of zidovudine and, to a lesser extent, that of its glucuronide, were decreased by a low dose of trimethoprim and trimethoprim-sulphamethoxazole. The fraction of the dose excreted as the parent compound, as well as the metabolic ratio also decreased. The metabolic ratio can be considered a marker of metabolic induction or inhibition if the glucuronide is not metabolized further. Its decrease reflects the lowering of zidovudine renal clearance and not any change in zidovudine metabolism.

The absence of a significant change in the AUC ratio and in the non-renal clearance of zidovudine, together with the decrease in zidovudine glucuronide renal clearance suggests an increase in ZG elimination by an extra-renal route, possibly biliary excretion.

The decreases in renal clearance of zidovudine and ZG on treatment with both trimethoprim and trimethoprim-sulphamethoxazole, indicate that trimethoprim alone is responsible for the interaction. The interaction is probably due to inhibition of the tubular secretion of zidovudine and its glucuronide. Trimethoprim is transported by the organic cation system (Cacini, 1987; Cacini & Myrc, 1985) and because it impairs the renal excretion of zidovudine, this suggests that zidovudine is also transported by this system. However, zidovudine also has affinity for the organic anion transport system by which it is secreted (de Miranda *et al.*, 1989).

Renal clearance represents only 20–30% of the total clearance of zidovudine. Therefore, interactions at this level are not expected to be clinically important unless hepatic glucuronidation is also impaired by liver disease or inhibited by other drugs.

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