Pharmacokinetics of zidovudine and dideoxyinosine alone and in combination in children with HIV infection

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The pharmacokinetics of zidovudine (ZDV) and dideoxyinosine (ddI) were investigated following administration alone and in combination to children with symptomatic HIV disease. The children were studied on three separate occasions and received ZDV 200 mg m⁻², ddI 100 mg m⁻² or a combination of ZDV 200 mg m⁻² plus ddI 100 mg m⁻². The administration of ddI did not significantly alter ZDV pharmacokinetics. The area under the curve (AUC) was 14.2 ± 4.9 and 15.8 ± 7.2 µmol l⁻¹ h and elimination half-life (*t*_{1/2,z}) was 1.4 ± 0.4 and 1.2 ± 0.2 h in the absence and presence of ddI respectively. The peak concentration (*C*_{max}), time to peak (*t*_{max}) and apparent oral clearance (CL/*F*) were also unchanged. The administration of ZDV had no significant effect on ddI *C*_{max}, *t*_{max}, *t*_{1/2,z}, or CL/*F*, however the AUC was reduced by 19% (5.9 ± 2.9 to 4.8 ± 2.7 µmol l⁻¹ h; *P* < 0.05). This study suggests that ZDV and ddI may be co-administered to children with symptomatic HIV disease without concern of a clinically relevant pharmacokinetic drug interaction.

Keywords zidovudine dideoxyinosine pharmacokinetics

Introduction

Zidovudine (3' azido-3'-deoxythymidine; ZDV) is a thymidine analogue antiretroviral drug which inhibits human immunodeficiency virus (HIV) replication, reducing mortality and the frequency of opportunistic infections when administered to adult patients with the acquired immunodeficiency syndrome (AIDS) or AIDS related complex (ARC) [1]. In children, there have been no controlled efficacy studies, but data from non-blind studies suggest clinical and immunological benefit with ZDV [2, 3]. However, ZDV has proved unsuccessful in controlling disease progression over extended periods of time and viral isolates with diminished *in vitro* sensitivity have emerged following ZDV treatment [4]. A strategy to enhance the effectiveness of antiretroviral therapy and delay the emergence of drug resistance may include the combination of ZDV and another reverse transcriptase inhibitor, dideoxyinosine (ddI), as ZDV resistant isolates do not exhibit cross resistance to ddI [5]. The combination of ZDV and ddI raises the possibility of a drug interaction and studies in adults have produced conflicting results. Preliminary work suggesting the possibility of increased toxicity when ZDV and ddI

were coadministered [6], was not confirmed by a subsequent study of combination therapy in adults using variable doses of ZDV and ddI [7]. We have recently described in adults a significant increase in the area under the plasma ZDV concentration-time curve and prolongation of the elimination half-life of ZDV in the presence of ddI (sachet preparation) and the absence of any effect of ZDV on ddI kinetics [8]. In this study we have investigated the pharmacokinetics of ZDV and ddI when administered alone and in combination to children with symptomatic HIV disease.

Methods

Patients

Eight male patients, aged 3 to 14 years, with HIV infection participated in this study. Three of the children had haemophilia and acquired HIV from

infected Factor VIII concentrates. The remaining children had been vertically infected. Five children had AIDS, three had symptomatic HIV disease. All patients had normal hepatic and renal function. None of the children had a history of pancreatitis and all had normal serum amylase levels. Current medications included ZDV or ddI and cotrimoxazole for *Pneumocystis carinii* pneumonia prophylaxis. Four children also received monthly intravenous immunoglobulin. None was taking any medications known to interfere with ZDV or ddI pharmacokinetics. Approval for the study was obtained from the local Ethics Committees and the parents of each child provided written informed consent.

Eight children were studied on three occasions separated by at least 24 h. The children were randomised to receive ZDV 200 mg m⁻², ddI 100 mg m⁻² or a combination of ZDV 200 mg m⁻² plus ddI 100 mg m⁻². On the combination study day ZDV syrup (10 mg ml⁻¹) was followed immediately by the ddI tablet. The children omitted their regular medications for 24 h prior to each study day and attended following an overnight fast. Once the study commenced they were encouraged to drink fluids but remained fasted for a further 2 h. An indwelling intravenous cannula was inserted in the cubital fossa for blood sampling. Medication was then administered and blood samples taken at 0, 15, 30, 45, 60, 90, 120, 240 and 360 min after dosage. All samples were centrifuged immediately to minimise the metabolism of ddI by erythrocytes [9]. Separated plasma was heated at 58°C for at least 30 min to inactivate HIV [10] and stored at -80°C until analysed.

Drug analysis

For the assay of ZDV, plasma was diluted 1:100 with blank plasma and mixed for 10 min. Aliquots of plasma were analysed using a commercially available radioimmunoassay kit (Sigma, Poole, UK) with the method being modified to reduce volumes of the reagents but with all other procedures remaining as given in the kit. In brief 3.5 nCi [³H]-ZDV and rabbit anti-ZDV antiserum was added to aliquots of diluted plasma and incubated at room temperature for 1 h. Immunoprecipitation reagent (anti-rabbit IgG antiserum) was added and the tubes were centrifuged (2000 g, 15 min, 4°C). The supernatant was discarded and the pellet redissolved in 0.1 N hydrochloric acid. Aliquots of the dissolved pellet were subjected to radiometric analysis. Intra-assay coefficients of variation were 9.9% and 8.0% for nominal concentrations of 5 and 15 ng ml⁻¹. Inter-assay coefficients of variation were 13.4 and 15.3% at the same concentrations. The assay had a limit of detection of 0.3 ng ml⁻¹. The cross reaction of ddI in the assay was <0.01%.

For the assay of ddI, plasma was diluted 1:100 with blank plasma and analysed using a commercially available radioimmunoassay kit (Sigma) as previously described [8]. The overall coefficients of variation of 1.25 and 2.5 ng ml⁻¹ ddI concentrations were <15%. The assay had a limit of detection of 0.1

ng ml⁻¹. The cross reaction of ZDV in the assay was <0.01%.

Data analysis

Values of $C_{\max}$ (μmol l⁻¹, μM) and $t_{\max}$ (h) were determined for ZDV and ddI directly from the data. The elimination rate constant (λ_z) was calculated by linear regression of the terminal portion of the log plasma drug concentration-time curve using the method of least squares. The terminal elimination half-life ($t_{1/2,z}$) was calculated from $\ln 2/\lambda_z$. Area under the concentration-time curve (AUC) values for ZDV and ddI were calculated using the linear trapezoidal rule with extrapolation from the last time point to infinity using $C(\text{last})/\lambda_z$; (the mean percentage of area that was extrapolated was approximately 5% for both ZDV and ddI). The oral clearance CL/F of ZDV and ddI was calculated from Dose/AUC . We assumed that a 40% change in AUC would be clinically relevant and performed a power analysis using known coefficients of variation from a previous pharmacokinetic study in adults [8]. This indicated that eight subjects should be sufficient to detect such a change (significance level of $\alpha = 0.05$ and a power of $1 - \beta = 0.85$).

Differences in kinetic parameters between the treatments were compared using either Student's two tailed paired *t*-test or the Wilcoxon signed-rank procedure (for $t_{\max}$). A *P* value of <0.05 was considered statistically significant.

Results

There was no significant difference in $C_{\max}$ (17.2 ± 9.1 vs 14.9 ± 7.3 μM; mean $\pm$ s.d.), $t_{\max}$ (0.25–0.5 vs 0.25–0.75 h; range), $t_{1/2,z}$ (1.4 ± 0.4 vs 1.2 ± 0.2 h), AUC (14.2 ± 4.9 vs 15.8 ± 7.2 μmol l⁻¹ h), or apparent oral clearance (36.7 ± 6.4 vs 36.0 ± 14.7 ml min⁻¹ kg⁻¹) for ZDV alone compared with ZDV plus ddI (Table 1). Similarly, there was no significant difference in $C_{\max}$ (5.1 ± 2.9 vs 4.0 ± 2.9 μM), $t_{\max}$ (0.5–0.75 vs 0.25–0.75 h), $t_{1/2,z}$ (0.9 ± 0.3 vs 1.0 ± 0.3 h) or apparent oral clearance (71.1 ± 59.9 vs 82.0 ± 53.4 ml min⁻¹ kg⁻¹) when comparing ddI alone with ddI plus ZDV. However, the AUC for ddI was reduced by 19% (5.9 ± 2.9 to 4.8 ± 2.7 μmol l⁻¹ h) in the presence of ZDV; this change just reached statistical significance ($P < 0.05$). Plasma concentration-time profiles for ZDV and ddI are shown in Figure 1 a and b respectively.

Discussion

ZDV is the antiretroviral agent of choice in the treatment of children with HIV infection and AIDS. The benefits of ZDV may be limited by toxicity, intolerance or refractory disease. In this setting ddI is an alternative therapy. A strategy to enhance the effectiveness of antiretroviral therapy and delay the emer-

Table 1 Pharmacokinetic parameters for zidovudine (ZDV) and ddI following oral administration of ZDV (200 mg m⁻²) and ddI (100 mg m⁻²) alone or in combination to eight children with symptomatic HIV disease. Data are presented as mean $\pm$ s.d. with the exception of $t_{\max}$, median (range). 95% CI: confidence intervals of the difference between the means for monotherapy vs combined therapy

	ZDV alone	ZDV + ddI	95% CI	ddI alone	ddI + ZDV	95% CI
$C_{\max}$ (μ M)	17.2 $\pm$ 9.1	14.9 $\pm$ 7.3	-8.89, 13.46	5.1 $\pm$ 2.9	4.0 $\pm$ 2.9	-0.68, 2.95
$t_{\max}$ (h)	0.25 (0.25-0.5)	0.5 (0.25-0.75)	-0.38, 0.07	0.5 (0.5-0.75)	0.5 (0.25-0.75)	-0.06, 0.25
$t_{1/2,z}$ (h)	1.4 $\pm$ 0.4	1.2 $\pm$ 0.2	-0.13, 0.61	0.9 $\pm$ 0.3	1.0 $\pm$ 0.3	-0.30, 0.07
AUC (μ mol l ⁻¹ h)	14.2 $\pm$ 4.9	15.8 $\pm$ 7.2	-6.54, 3.29	5.9 $\pm$ 2.9	4.8 $\pm$ 2.7	0.14, 2.06*
CL/F (ml min ⁻¹ kg ⁻¹)	36.7 $\pm$ 6.4	36.0 $\pm$ 14.7	-12.10, 13.45	71.1 $\pm$ 59.9	82.0 $\pm$ 53.4	-29.9, 8.0

*Significantly different $P < 0.05$ (Student's paired t -test).

Figure 1 Mean plasma concentration ($\pm$ s.d.) of a) ZDV and b) ddI in eight children with symptomatic HIV disease following a) ZDV 200 mg m⁻² alone (■) or in combination with ddI 100 mg m⁻² (◆). b) ddI 100 mg m⁻² alone (■) and in combination with ZDV 200 mg m⁻² (◆).

gence of drug resistance may be the main use of combination therapy [7, 11]. As ZDV undergoes extensive hepatic glucuronidation [12] and ddI is catabolized by purine nucleoside phosphorylase to hypoxanthine and uric acid [9] a metabolic interaction would seem unlikely. In human liver microsomes

in vitro, ddI failed to inhibit ZDV glucuronidation at concentrations up to 10 mM [13]. This is consistent with a study in rats in which ZDV and ddI were administered by intravenous injection alone and in combination. There was no alteration in kinetic parameters for either drug on coadministration [14]. However, studies in monkeys, an animal that serves as an appropriate model for the pharmacokinetics of both ZDV and ddI in humans, suggest that both renal and metabolic elimination of ZDV may be inhibited by ddI [15]. In adult patients with HIV disease Collier *et al.* [7] failed to demonstrate a pharmacokinetic drug interaction or increased toxicity when ZDV and ddI were coadministered. In a study of eight adult patients with HIV infection we found that the combination of ZDV and 250 mg sachet ddI resulted in an 18% increase in the elimination half-life of ZDV together with a 35% increase in AUC [8]. We speculated that the changes in ZDV kinetic parameters may reflect altered absorption (due to the ddI formulation which contains citrate phosphate buffer to enhance ddI absorption as ddI is acid labile [16]) and/or decreased metabolic clearance.

In the present study of eight children with symptomatic HIV disease, administration of ZDV 200 mg m⁻² (as a syrup) and ddI 100 mg m⁻² (tablet formulation with antacid) alone and in combination did not result in a significant alteration in ZDV pharmacokinetic parameters although the AUC of ddI was significantly reduced in the presence of ZDV. Therefore the findings from this study suggest that ddI in tablet form (unlike the sachet formulation) does not affect ZDV disposition. The reason for the small, but statistically significant change in ddI AUC in the presence of ZDV is unclear. We believe that ZDV and ddI can be coadministered to children with symptomatic HIV disease without concern for a clinically relevant drug interaction. This is consistent with a recent phase II study in children where ZDV and ddI in combination did not result in any additional toxicity [17].

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