Plasma levels of zidovudine twice daily compared with three times daily in six HIV-1-infected children

Alina S. Bergshoeff¹,², Pieter L. A. Fraaij³, Corrien Verweij¹,², Annemarie M. C. van Rossum³, Gwenda Verweel³, Nico G. Hartwig³, Ronald de Groot³ and David M. Burger¹,²*¹Department of Clinical Pharmacy, University Medical Center, Nijmegen; ²Nijmegen University Center for Infectious Diseases, Nijmegen; ³Department of Pediatrics, Erasmus MC/Sophia, Rotterdam, The Netherlands

Received 8 August 2004; returned 20 September 2004; revised 30 September 2004; accepted 1 October 2004

Objectives: Zidovudine is often administered every 12 h in HIV-infected children, but so far no pharmacokinetic data are available for the administration of this agent every 12 h. We have evaluated the plasma pharmacokinetics of zidovudine administered every 8 h versus every 12 h in HIV-1-infected children.

Methods: In HIV-1-infected children who switched from zidovudine every 8 h to every 12 h, a pharmacokinetic curve was recorded both before and after the switch. Zidovudine plasma levels were measured by HPLC. Pharmacokinetic parameters were calculated by non-compartmental methods.

Results: Six HIV-1-infected children [median age (range) 7.8 (2.5–13.4) years] were included. In these patients, geometric mean ratios of AUC₀–2₄ and \( C_{\text{max}} \) for zidovudine every 12 h versus every 8 h were not significantly different from 1.0.

Conclusions: The plasma pharmacokinetic parameters of zidovudine taken every 8 h and every 12 h were not significantly different and therefore suggest bioequivalence of these two dose frequencies.

Keywords: pharmacokinetics, paediatrics, pharmacology

Introduction

Zidovudine was the first drug licensed for treatment of HIV infection. It is recommended as a component of highly active antiretroviral treatment (HAART) and in the prophylaxis of perinatal transmission of HIV.¹,² Current guidelines, such as PENTA, indicate a paediatric dose range for zidovudine of 90–180 mg/m² every 6 h or every 8 h. Meanwhile, zidovudine is also increasingly used every 12 h. However, in children, except for neonates and infants, no published data exist on the pharmacokinetics of zidovudine every 8 h or every 12 h.³–⁵ Considering their common use in children, the pharmacokinetics of these regimens should be characterized in paediatric patients. We report here the plasma pharmacokinetics of zidovudine every 8 h and every 12 h in six HIV-1-infected children.

Methods

This was a retrospective analysis of pharmacokinetic data from HIV-1-infected children in the age range 1–18 years, who were included in an ongoing study on the simplification of HAART conducted in our centre (inclusion August 2000–January 2003). Briefly, children were offered the possibility of changing their every 8 h HAART into fully every 12 h HAART. Antiretroviral medication prior to the switch consisted of zidovudine 120 mg/m² every 8 h with indinavir 600 mg/m² every 8 h and lamivudine 4 mg/kg every 12 h. After the switch, children received zidovudine 180 mg/m² every 12 h with indinavir/ritonavir 500/100 mg/m² every 12 h and lamivudine 4 mg/kg every 12 h. Zidovudine was administered as capsules of 100 mg or 250 mg, as tablets of 300 mg or as oral solution containing 10 mg/mL (Retrovir; AZT). Written informed consent was obtained from patients or carers prior to enrolment. Intensive pharmacokinetic sampling of all antiretroviral drugs was performed at steady state, prior to and >2 weeks after switch to the every 12 h regimen. Here we describe the pharmacokinetics of zidovudine in patients who changed from taking zidovudine every 8 h to every 12 h.

The plasma concentrations of zidovudine were determined by validated HPLC assay with UV detection [lower limit of quantification, 0.017 mg/L; accuracy 99%–101%, intra- and interday coefficients of variation 1.5%–2.0% and 1.5%–2.2%, respectively.
Zidovudine twice daily in children

Six patients were enrolled (five girls, one boy) of median age 7.8 years (range 2.5–13.4). The median number of samples per pharmacokinetic curve was seven for the every 8 h regimen, and 7.5 for the every 12 h regimen. GMRs of pharmacokinetic parameters for zidovudine every 12 h versus every 8 h were calculated, from which geometric mean ratios (GMR) with 90% confidence intervals (CI) were obtained. A 90% CI of GMR containing 1.0 was considered as reflecting similarity of both regimens. Results were compared with literature data on adults.

Results

Six patients were enrolled (five girls, one boy) of median age 7.8 years (range 2.5–13.4). The median number of samples per pharmacokinetic curve was seven for the every 8 h regimen, and 7.5 for the every 12 h regimen. GMRs of pharmacokinetic parameters for zidovudine every 12 h versus every 8 h did not show significant differences between either regimen, but were characterized by wide CI. In our study, except for $C_{\text{max}}$ of the every 12 h regimen, zidovudine levels were slightly higher than in adults using zidovudine every 8 h or every 12 h (Table 1 and Figure 1). Zidovudine every 12 h did not result in a higher $C_{\text{max}}$ than zidovudine every 8 h. No correlation was found between zidovudine pharmacokinetic parameters ($\text{AUC}_{0–24}$, $C_{\text{max}}$, $C_{\text{min}}$, $\text{CL/F} \cdot \text{m}^2$, and $t_{1/2}$) and age, body weight or body surface area ($P$ values all $>0.05$). However, zidovudine $t_{1/2}$ was inversely

### Table 1. Pharmacokinetics of zidovudine every 12 h and every 8 h in HIV-1-infected children and historical data of zidovudine in adults

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Children using zidovudine 120 mg/m² every 8 h in current study ($GM \pm 90% \ CI$)</th>
<th>Children using zidovudine 180 mg/m² every 12 h in current study ($GM + 90% \ CI$)</th>
<th>Zidovudine every 12 h versus every 8 h in current study ($GMR + 90% \ CI$)</th>
<th>Zidovudine every 12 h in current study ($GM + 90% \ CI$)</th>
<th>Zidovudine every 12 h in current study ($GM + 90% \ CI$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AUC}_{0–24} (\text{mg} \cdot \text{L}^{-1} \cdot \text{h})$</td>
<td>5.24 (2.73–7.95)</td>
<td>4.72 (3.50–6.36)</td>
<td>0.90 (0.52–1.56)</td>
<td>0.90 (0.52–1.56)</td>
<td>0.90 (0.52–1.56)</td>
</tr>
<tr>
<td>$C_{\text{max}} (\text{mg} / \text{L})$</td>
<td>0.96 (0.55–1.70)</td>
<td>1.04 (0.69–1.57)</td>
<td>1.08 (0.62–1.88)</td>
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</tr>
<tr>
<td>$C_{\text{min}} (\text{mg} / \text{L})$</td>
<td>0.18 (0.05–0.71)</td>
<td>0.26 (0.10–0.67)</td>
<td>0.32 (0.14–0.74)</td>
<td>0.32 (0.14–0.74)</td>
<td>0.32 (0.14–0.74)</td>
</tr>
<tr>
<td>$\text{CL/F} \cdot \text{m}^2 (\text{L/h} \cdot \text{m}^2)$</td>
<td>63.3 (46.6–85.8)</td>
<td>79.5 (60.3–104.8)</td>
<td>1.26 (0.83–1.90)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>$t_{1/2} (\text{h})$</td>
<td>1.31 (0.99–1.72)</td>
<td>1.15 (0.90–1.47)</td>
<td>0.88 (0.71–1.10)</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

NA, not available; ND, not determined; GM, geometric mean; GMR, geometric mean ratio; CI, confidence interval; s.e.m., standard error of the mean; AUC, area under the plasma concentration–time curve; $C_{\text{max}}$, peak plasma level; $C_{\text{min}}$, plasma trough level; CL/F, relative apparent oral clearance; $t_{1/2}$, terminal plasma half-life.

**Figure 1.** (a) $\text{AUC}_{0–24}$ and (b) $C_{\text{max}}$ of zidovudine every 12 h versus every 8 h in six children who switched from zidovudine every 8 h (TID) to every 12 h (BD).
correlated with age for both the every 12 h regimen and the every 8 h regimen ($r^2 = -0.78$ and $-0.69$, $P$ values 0.019 and 0.042, respectively).

**Discussion**

This study presents the first pharmacokinetic data of zidovudine every 12 h compared with every 8 h in children above the infant age. The pharmacokinetic parameters of zidovudine every 12 h compared with every 8 h did not reveal significant differences, suggesting equivalence of both regimens in terms of plasma pharmacokinetics. The observed tendency for higher plasma levels in children than in adults could be due to the higher paediatric zidovudine dose per body weight: 360 mg/m²/day equals 13 mg/kg/day in an average child with 1 m² body surface area and weighing 28 kg, which is higher than the adult dose (600 mg/day = 8.6 mg/kg/day in an adult weighing 70 kg). Also, zidovudine every 12 h did not result, as expected with lower dose frequency, in a higher $C_{\text{max}}$ than every 8 h. The pharmacokinetic parameters of zidovudine were highly variable, probably as a result of the small sample size. Therefore, these findings should be confirmed in a larger number of patients. Zidovudine $AUC_{0-24}$, $C_{\text{max}}$ and $CL/F\cdot m^2$ were independent of age, body weight or body surface area. This is in accordance with literature data, which generally indicate that zidovudine $CL/F\cdot m^2$ increases most strongly during the first weeks of life, with literature data, which generally indicate that zidovudine metabolism during childhood. Remarkably, as stated above, this higher elimination rate was not reflected in a lower $AUC_{0-24}$ or $C_{\text{max}}$ or higher $CL/F\cdot m^2$ in older children. Although this finding should be considered cautiously because of the small number of patients in our study, an explanation—also described in relation to premature infants—could be decreased zidovudine absorption or increased first-pass metabolism in younger children, resulting in no net difference of $AUC_{0-24}$, $C_{\text{max}}$ or $CL/F\cdot m^2$ between younger and older children.

In conclusion, in this group of six HIV-1-infected children, the pharmacokinetics of zidovudine every 12 h were not statistically different from every 8 h, suggesting bioequivalence of both regimens. These findings need confirmation in studies with a larger sample size. Finally, the efficacy of both regimens in children should be evaluated in a comparative study.

**Acknowledgements**

Technicians of the Department of Clinical Pharmacy, University Medical Center, Nijmegen, are kindly acknowledged for processing and analysis of the plasma samples. Study nurses of the Department of Pediatrics, Erasmus MC/Sophia, Rotterdam, are kindly acknowledged for blood drawings. No financial support was received for this study.

**References**