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Pharmacokinetics of Zidovudine Dosed Twice Daily According to World Health Organization Weight Bands in Ugandan HIV-infected Children

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Abstract: Data on zidovudine pharmacokinetics in children dosed using World Health Organization weight bands are limited. About 45 HIV-infected, Ugandan children, 3.4 (2.6–6.2) years, had intensive pharmacokinetic sampling. Geometric mean zidovudine AUC_{0-12h} was 3.0 h.mg/L, which is higher than previously observed in adults, and was independently higher in those receiving higher doses, younger and underweight children. Higher exposure was also marginally associated with lower hemoglobin.

Key Words: zidovudine, pharmacokinetics, HIV, children, Africa

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Current World Health Organization (WHO) 2010 guidelines for the treatment of HIV-infected children recommend 2 nucleoside reverse transcriptase inhibitors as part of first-line combination antiretroviral therapy (ART).[1] For infants/children, the preferred nucleoside reverse transcriptase inhibitor backbone is twice-daily lamivudine + zidovudine, which is effective, inexpensive and available as fixed-dose combination scored adult tablets (Combivir, GlaxoSmithKline, London, United Kingdom),[2] which can be split for pediatric dosing, or as generic dual or triple (with nevirapine) pediatric FDCs. However, although studies have investigated the pharmacokinetics of the current lamivudine doses,[3] surprisingly most zidovudine pharmacokinetic data are based on old 6–8 hourly and/or higher dosing.[4,5] Data on zidovudine pharmacokinetics and pharmacodynamics at currently recommended lower/less frequent doses in children remain sparse, particularly in African children.[6] Pharmacokinetic-pharmacodynamic studies are particularly important as anemia is a common, plausibly dose-related, toxicity.[7,8]

As ~90% HIV-infected children needing ART are in Africa, we investigated zidovudine exposure in Ugandan, HIV-infected children receiving WHO-recommended twice-daily, weight band-based dosing (not studied to date).

METHODS

ARROW was an open randomized trial comparing monitoring and first-line ART strategies in HIV-infected Ugandan/Zimbabwean children eligible for and initiating ART.[9] Allocation to zidovudine-containing regimens or not was part of the first-line ART strategy randomization.[9] Once stable on ART (>24 weeks after initiation) children from 2 Ugandan ARROW centers (Joint Clinical Research Centre, Kampala and Paediatric Infectious Disease Centre, Mulago, Kampala) were approached for additional consent to participate in 2 intensive crossover pharmacokinetic substudies. The first compared twice- versus once-daily lamivudine and abacavir in children 3–12 years of age, before and 4 weeks after move to once-daily dosing, 36 weeks after ART initiation.[3] All children were taking efavirenz; some were also taking zidovudine as a 4th drug at the first (36-week) pharmacokinetic sampling day. The second substudy compared twice-daily zidovudine, lamivudine and abacavir as syrups versus tablets in children 1–4 years of age, at and 4 weeks after moving from syrups to tablets[6] [median interquartile range (IQR) 56 (40–70) weeks on ART].

This analysis included all available zidovudine pharmacokinetic data from both substudies. Children on concomitant medication which could interfere with ART or who had illnesses that could influence ART pharmacokinetics were excluded, as were children who reported missing any ART dose in the previous 3 days. All caretakers provided fully informed written consent. The pharmacokinetic substudies were approved by the Ethics Committee from each centre.

Zidovudine was dosed twice daily as syrups or halved or whole 300 mg solid formulation and scored fixed-dose combination tablets (provided by GlaxoSmithKline; Table, Supplemental Digital Content, http://links.lww.com/INF/B733). Doses followed WHO 2006 recommendations, except that children weighing 12–15 kg received 240 mg zidovudine syrup daily instead of 220 mg, children weighing 20–21 kg on lamivudine/zidovudine FDCs received 300 mg zidovudine rather than 450 mg and children 21 to <25 kg received 450 mg zidovudine to harmonize with the lamivudine weight band. Blood samples of 1.5 mL were taken at t = 0, 1, 2, 4, 6, 8 and 12 hours after observed ART intake. Breakfast (mostly milk/milky tea with samosas/bread/chapati) was provided 2 hours post morning dose. Plasma concentrations were assayed by a validated high-performance liquid chromatography-tandem mass spectrometry method,[10] with lower limit of quantification 0.0025 mg/L, by Worldwide Bioanalysis, GlaxoSmithKline, Research Triangle Park, North Carolina. Zidovudine pharmacokinetic

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parameters [C_{12h}, C_{max}, $AUC_{0–12h}$, $t_{½}$, oral clearance (CLF)] were calculated using WinNonlin version 5.2 (Pharsight Corporation, Mountain View, CA). To explore predictors of zidovudine exposure using WHO weight band dosing, associations between zidovudine $AUC_{0–12h}$ and sex, age, dose (mg/m^2), weight- and height-for-age and formulation were investigated using multivariable mixed models including a child-level random effect (STATA version 11.1, STATA Corp, College Station, TX).

RESULTS

Zidovudine pharmacokinetic data were included from 45 children (17 (38%) male). Twenty-eight (62%) children 1–4 years of age had 2 pharmacokinetic profiles (1 each on syrup and tablets) and 17 (38%) children 3–12 years of age had 1 profile on tablets. One child had $C_{0h} > 3·C_{12h}$ and was excluded, leaving 72 pharmacokinetic profiles available for analyses. Median (IQR) age and weight at the first pharmacokinetic day were 3.4 (2.6–6.2) years and 12.6 (12.3–18.0) kg, respectively. Median (IQR) weight-for-age and height-for-age z-scores were −1.09 (−1.62 to −0.56) and −1.85 (−2.68 to −1.20), indicating moderate wasting and stunting. Of the 72 evaluable profiles, median (IQR) zidovudine morning and total daily doses were 242 (218–278) and 466 (432–546) mg/m^2, respectively [10 (9.4–12.2) and 20 (18.5–23.9) mg/kg respectively]. Eight (11%), 20 (27%) and 36 (50%) profiles were from children on 100 mg syrup, 120 mg syrup and 150 mg lamivudine/zidovudine fixed-dose combination tablets twice daily, respectively; and 8 (11%) were on 300 mg morning and 150 mg evening tablets.

The geometric mean (GM; 95% confidence interval) $AUC_{0–12h}$, $C_{max,}$ C_{12h}, $t_{½}$ and CLF, and CLF/kg was 3.0 (2.7–3.3) h.mg/L, 1.8 (1.6–1.9) mg/L and 0.009 (0.007–0.010) mg/L, 2.3 (2.1–2.5) h, 48.6 (43.1–54.6) L/h and 3.5 (3.2–3.8) L/h.kg, respectively (Fig. 1A) with CV% of 40%, 42%, 70%, 18%, 54% and 44%, respectively. Zidovudine $AUC_{0–12h}$ was 27–150% higher than previously reported in adults.[2,11] GM C_{max} were 1.84 mg/L and 1.58 mg/L in children less than and greater than 4 years ($P = 0.12$, rank sum), respectively.

In multivariable models, higher zidovudine exposure ($AUC_{0–12h}$) was independently associated with higher dose, younger age and lower weight-for-age, with the latter 2 factors independently associated with CLF. $AUC_{0–12h}$ was 0.43 h.mg/L higher for every 50 mg/m^2 higher zidovudine dose (95% confidence interval:

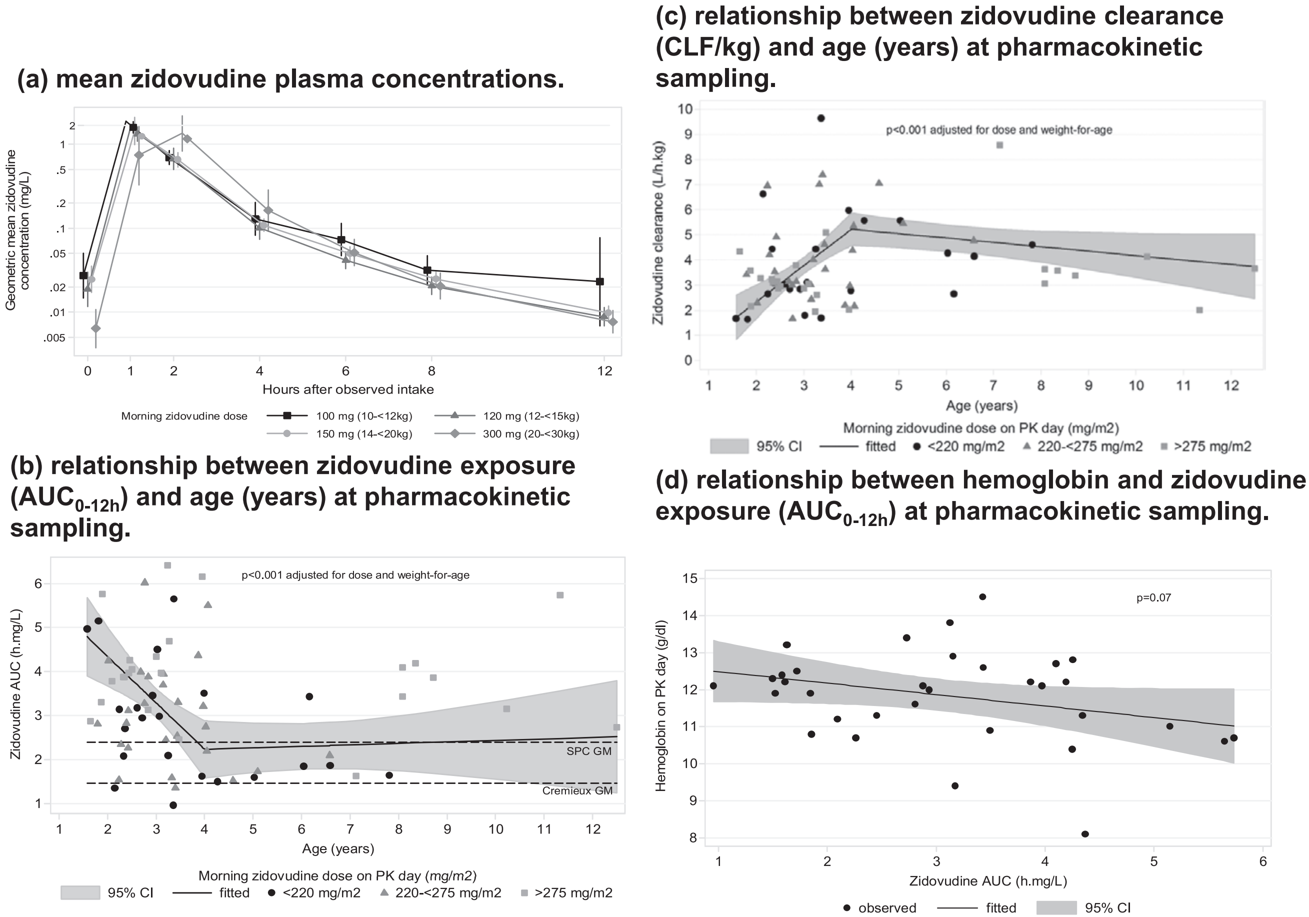

FIGURE 1. Mean zidovudine concentrations, exposure, age and hemoglobin at pharmacokinetic sampling. A) Mean zidovudine plasma concentrations. B) Relationship between zidovudine exposure [area under the concentration–time curve 0–12 hours postdose ($AUC_{0–12h}$)] and age (years) at pharmacokinetic sampling. C) Relationship between zidovudine clearance (CLF/kg) and age (years) at pharmacokinetic sampling. D) Relationship between hemoglobin and zidovudine exposure [area under the concentration–time curve 0–12 hours postdose ($AUC_{0–12h}$)] at pharmacokinetic sampling. Note: In panel A), children receiving 450 mg daily received 300 mg zidovudine in the morning and are included in this group. In panel B), fitted effect of age is shown for a child with median weight-for-age (–1.09) and median dose (242 mg/m^2). Points demonstrate the relationship between age and dose which is adjusted for within the multivariable model.

0.15–0.71; P = 0.003). Associations between age and zidovudine exposure varied across the age range (test for nonlinearity P = 0.001). Independent of the dose effect, zidovudine exposure was 1.06 (0.48–1.63) h.mg/L lower and clearance 1.44 (0.67–2.22) L/h.kg higher for every year up to 4 years of age (P < 0.001), but there was no association for >4 years (exposure P = 0.72, CLF/kg; P = 0.14; Fig. 1B,C). Thus, for the same dose in mg/m^2, lower clearance meant that youngest children had higher plasma zidovudine exposure. Exposure was 0.72 (0.30–1.13) h.mg/L lower and clearance 0.80 (0.24–1.36) L/h.kg higher for every unit higher weight-for-age (P = 0.001 and P = 0.005, respectively). Adjusted for these factors, there was no independent effect on exposure/clearance of sex (P = 0.56/0.32), height-for-age (P = 0.57/0.57) or formulation (syrups/tablets; P = 0.75/0.76; P = 0.30/0.86 in children under 4 years of age). There was a trend toward higher C_{max} in children <4 years [GM = 1.9 mg/L (95% confidence interval: 1.7–2.1)] vs. >4 years [GM = 1.5 mg/L (1.3–1.9) P = 0.096]. Thirty-seven children had viral load (VL) measured within 4 weeks of pharmacokinetic sampling day. Thirty-two (86%) had VL <80 c/mL; only 1 (3%) had VL >400 c/mL (17,174 c/mL). This child had an $AUC_{0–12h}$ of 3.7 h.mg/L.

Thirty-four children had hemoglobin assayed within 1 day of the pharmacokinetic sampling. There was marginal evidence for 0.31 g/dL lower hemoglobin per 1 h.mg/L higher zidovudine $AUC_{0–12h}$ (−0.65 to +0.03; P = 0.07; Fig. 1D).

DISCUSSION

Here, zidovudine exposure in Ugandan children 1–12 years of age dosed twice daily according to WHO 2006 weight bands was higher than exposure previously reported in adults receiving the standard dose of 300 mg zidovudine twice daily.[2,11] Exposure was also higher (GMs were 2.36 and 1.58 h.mg/L) than in the only 2 previous pediatric zidovudine pharmacokinetic studies,[5,12] which used lower doses than our study (Table, Supplemental Digital Content, http://links.lww.com/INF/B733 and 360 vs. 360–480 mg/m^2/d, respectively). Subsequent 2010 WHO guidelines[1] have further increased the recommended zidovudine dose for all children except those weighing 15–20 or >30 kg (Table, Supplemental Digital Content, http://links.lww.com/INF/B733), without new evidence, but reflecting concerns that children had often been under dosed with antiretrovirals. Thus, exposure in children currently receiving zidovudine in Africa is likely to be even higher than observed here.

In addition to the expected association between higher zidovudine exposure and mg/m^2 dose, we found strong independent evidence that higher exposure was associated with lower age in children <4 years and with lower weight-for-age. While 1 study suggested that zidovudine clearance increased most rapidly during the first weeks of life, reaching adult levels at 2 years of age,[8] a small study in 6 Dutch children[5] showed elimination rate increased with age between 2 and 14 years, implying further maturation of metabolism during childhood. Similarly, we found exposure from the same mg/m^2 dose decreased in children from 1 to 4 years. An alternative explanation might be a greater absorption in younger children; although we did not find evidence that liquid versus solid formulations might cause this, there was a trend to higher C_{max} in younger children. We did not find any association between exposure and age among 19 children who were >4 years of age, but moderate-to-large variability may have obscured this.

Data relating zidovudine exposure and toxicity are limited.[7,8] Although only 34 children had paired hemoglobin and pharmacokinetic measurements, we found marginal evidence for lower hemoglobin values with higher zidovudine exposure. This is similar to a previous population pharmacokinetic study,[8] which found mild anemia in 23% of those with average zidovudine concentration >350 ng/mL (vs. 8% without). However, these children were receiving zidovudine as only mono or dual therapy; chronic HIV-related anemia is common in HIV disease, so the contribution of replicating HIV to these findings is unclear. Furthermore, all but 2 hemoglobin values in our study were in the normal range (1 grade 1 to 1 grade 2 toxicity). Whether higher exposure increases the risk for more severe toxicity over the longer term is unknown.

A study limitation is that we included only Ugandan (East African) children, thus limiting generalizability to other populations where host genetics may result in different pharmacokinetics. A population pharmacokinetic study including data from 100 children from 6 pediatric trials, including this study, is ongoing and is expected to provide further insight in the pharmacokinetics and potential cofactors that may impact the pediatric pharmacokinetics of zidovudine. Another limitation is that the true C_{max} (T_{max} is 0.5 hours)[2] could have been missed and consequently $AUC_{0–12h}$ might be underestimated. Lastly, because of challenges in sampling relatively young children over 24 h, we were unable to directly estimate the impact of unequal morning and evening dosing in those weighing 20–30 kg.

In summary, zidovudine is a common component of first-line pediatric ART, especially in resource-limited countries and only limited data are available on the widely applied twice-daily dosing regimen. Children dosed following WHO 2010 guidelines, younger children and those with low weight-for-age are likely to have even higher zidovudine exposure than that observed here and substantially higher than previously reported in adults. Our findings suggest that this higher exposure could be associated with greater suppression of hemoglobin levels within the normal range and probably with no change in efficacy, because viral load suppression was already very good using WHO 2006 dosing. The impact on severe anemia warrants further investigation, particularly with regards to current WHO 2010 dosing.

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