

Pharmacokinetics of Nevirapine in HIV-infected Infants with Body Weight 3–6 kg Taking Pediatric Fixed Dose Combination Tablets

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Background: We previously reported 12h pharmacokinetic (PK) profiles of nevirapine (NVP), stavudine (d4T) and lamivudine (3TC) in HIV-infected African children after taking fixed dose combination (FDC) antiretroviral tablets (Triomune Baby (50mg NVP; 6mg d4T; 30mg 3TC) and Junior (double Baby dose)(L'homme et al, AIDS 2008). However, this study included only 2 children with body weight (BW) 3-6 kg; we therefore undertook PK evaluations in 14 additional children weighing 3-6 kg.

Methods: 16 HIV-infected children aged 1 month or older, weighing 3-6 kg, and fulfilling WHO criteria for initiating treatment were included. Children were admitted for a 12h PK sampling session at least 4 weeks after starting treatment. Samples were taken at t=0, 2, 6 and 12h after observed intake of 1 tablet Triomune Baby. NVP plasma concentrations were determined using HPLC with UV detection. PK parameters (AUC, C_{max}, C_{min}) were determined using noncompartmental methods.

Results: One child was excluded due to nonadherence. The median (interquartile range) age, BW and daily NVP dose of the remaining 15 children (8 girls; 7 boys) were 5.3 (4.1-8.4) months, 5.3 (4.2-5.5) kg and 348 (324-386) mg/m², respectively. The mean (standard deviation) NVP AUC_{0-12h}, C_{max} and C_{min} were 78.7 (30.2) h.mg/L, 8.1 (2.4) mg/L, and 4.9 (2.6) mg/L, respectively. These values are higher than reported in adults, but are 15-20% lower than observed previously in Zambian children with BW >6 kg taking these paediatric FDCs. Of some concern, 4/15 (27%) children with BW 3-6 kg had a subtherapeutic NVP C_{min} (defined as <3.0 mg/L) compared to only 3/63 (5%) children with body weight >6 kg (p = 0.02, Exact Test). Whilst children aged <5 months appeared to have a higher risk for a subtherapeutic NVP C_{min} than those 5 months or older, numbers were too small to reach statistical significance (3/6 (50%) vs. 1/9 (11%); p=0.24); note, dose range in those <5 months was 324-406mg/m².

Conclusions: Exposure to NVP in African HIV-infected children with low BW taking FDC tablets appears on average to be adequate, but due to large intersubject variability a relatively high proportion of children had subtherapeutic NVP C_{min} levels, particularly those aged <5 months. As infants <5 months may be at risk for low NVP exposure for only a short time after initiating treatment, the clinical consequences of such low C_{min} may be minor, but require further evaluation.

Keywords: Nevirapine, Fixed Dose Combination, pharmacokinetics, children, Zambia

Introduction

Last year we reported a 12 hour pharmacokinetic (PK) study of nevirapine (NVP), stavudine (d4T) and lamivudine (3TC) in Zambian HIV-infected children after taking fixed dose combination (FDC) antiretroviral tablets Triomune Baby (50mg nevirapine, 6mg stavudine and 30mg lamivudine) and Triomune Junior (double Baby dose)¹. These tablets have higher nevirapine to NRTI dose ratios than adult FDCs in accordance with paediatric dose recommendations to prevent nevirapine underdosing.

However, this study included only 2 children with body weight (BW) 3-6 kg. We therefore undertook PK evaluations in an additional 14 children weighing 3-6 kg for a PK substudy.

Methods

16 children aged 1 month or older, weighing 3-6 kg, and fulfilling WHO criteria for initiating treatment were included. Full nevirapine dosing was chosen to aim for daily doses of 300-400 mg/m² using estimated body surface area (BSA) for weight in the weight band 3-6 kg. Daily stavudine and lamivudine were targeted to 2 and 8 mg/kg respectively². According to these guidelines children in weight band 3-6 kg get one tablet of Triomune Baby twice daily. At least four weeks after starting Triomune Baby a 12 hour PK sampling session was done. Samples were taken at t = 0, 2, 6 and 12 hours after observed intake of one tablet Triomune Baby.

Results: demographics

One child was excluded because C₀ suggested poor adherence.

Table 1: Baseline demographics and ARV therapy dosing by baseline weight

	Children in weight band 3-6 kg
N	15
sex, female	8 (53%)
age, months	5.3 (4.1 - 8.4)
weight, kg	5.3 (4.2 - 5.5)
weight-for-age z-score	-3.23 (-4.61 to -2.37)
height-for-age z-score	-3.30 (-5.44 to -2.70)
BMI-for-age z-score	-1.19 (-3.53 to -0.20)
CD4-for-age z-score	-2.39 (-3.48 to -1.93)
CD4%	15.3 (8.1 - 22.0)
WHO stage 1	1* (7%)
WHO stage 3	7 (47%)
WHO stage 4	7 (47%)
Daily prescribed nevirapine dose (100 mg), mg/m ²	348 (324-386)
Daily described stavudine dose (12 mg), mg/kg	2.3 (2.2-2.9)
Daily described lamivudine dose (60 mg), mg/kg	11.3 (10.9-14.2)

child started ART on the basis of low CD4 count

Values are n (%) for categorical variables and median (interquartile range, IQR) for continuous variables.

Results: pharmacokinetics [1]

In table 2, pharmacokinetic parameters are compared with data from the previous study in higher weight bands and with data from adults.

- Pharmacokinetic parameters of nevirapine were 15-20% lower in the 3-6kg weight band (not or marginally statistically significantly different to >6 kg weight bands), but were higher than those previously reported in adults in both groups.
- Variability in nevirapine C_{min} levels in this cohort was comparable to the variability in children with body weight >6 kg, but greater than historical data from adults.
- PK parameters of stavudine and lamivudine were broadly comparable to those previously reported in children with body weight > 6 kg and adults.

Table 2: Pharmacokinetic parameters of nevirapine, stavudine and lamivudine

	Weight band 3 - 6 kg (n=15)	Weight bands > 6 kg (n=63*)	p (ranksum)	Literature data adults
Nevirapine				
C _{min} (mg/L)	4.93 (2.36, 7.06) [2.63]	6.10 (4.15,7.00) [2.95]	p=0.18	3.7 ³
C _{max} (mg/L)	8.10 (6.08, 9.74) [2.41]	10.06 (7.87, 11.40) [3.82]	p=0.05	5.7 ⁶
AUC _{0-12h} (h.mg/L)	78.74 (54.67, 106.75) [30.22]	95.26 (70.84, 107.67) [39.08]	p=0.14	54.5 ³
Stavudine*				
C _{min} (mg/L)	<0.015 (<0.015,<0.015) [-]	<0.015 (<0.015, <0.015) [-]	-	0.009 ⁴
C _{max} (mg/L)	0.27 (0.21, 0.36) [0.11]	0.45 (0.33, 0.52) [0.15]	p<0.001	0.54 ⁴
AUC _{0-12h} (h.mg/L)	0.94 (0.74, 1.11) [0.32]	1.06 (0.80, 1.33) [0.40]	p=0.54	1.28
Lamivudine*				
C _{min} (mg/L)	0.13 (0.08, 0.17) [0.05]	0.09 (0.06, 0.12) [0.05]	p=0.005	0.09 ⁵
C _{max} (mg/L)	1.46 (0.52, 2.13) [0.85]	1.35 (0.90, 1.60) [0.68]	p=0.59	1.2 ⁵
AUC _{0-12h} (h.mg/L)	7.00 (3.86, 9.27) [3.71]	5.46 (3.78, 6.87) [2.24]	p=0.16	4.7 ⁵

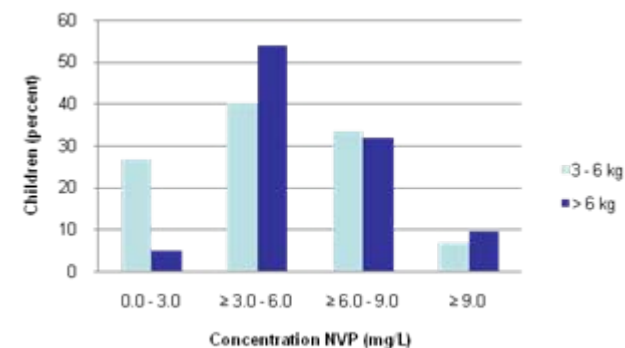
* d4T and 3TC analysis failed for one child.

Values are mean (interquartile range) [SD]

Results: pharmacokinetics [2]

- Four of 15 (27%) children in the 3-6kg weight band had a subtherapeutic nevirapine C_{min} level (<3.0 mg/L) 12 hours after intake compared to only 3/63 (5%) children with body weight >6 kg (p = 0.02, Exact test).
- Children aged <5 months (3/6 (50%)) appeared to have a higher risk for a subtherapeutic nevirapine C_{min} level than children 5 months or older (1/9 (11%)) although this did not reach statistical significance (p=0.24).
 - The 6 children <5 months were receiving 324-406 mg/m² nevirapine daily

Figure 1: Minimum concentrations of nevirapine in children weighing 3-6 kg vs. children weighing >6 kg



Conclusions

- Exposure to nevirapine in Zambian HIV-infected children taking Triomune Baby appears on average to be adequate.
- A large intersubject variability was found in nevirapine C_{min} concentrations of children weighing 3-6 kg.
- Four (27%) children with body weight 3-6 kg had a subtherapeutic nevirapine C_{min} levels (<3.0 g/L), particularly those aged <5 months.
- Clinical consequences of nevirapine exposure may be minor as infants will be <5 months for only a short time after initiating treatment, but further evaluation is required.
- Pharmacokinetic parameters of stavudine and lamivudine were comparable to those previously reported in children in higher weight bands.