Eur J Med Res (2006) 11: 377-380

NEED FOR THERAPEUTIC DRUG MONITORING IN HIV-1 INFECTED CHILDREN RECEIVING EFAVIRENZ DOSES ACCORDING TO INTERNATIONAL GUIDELINES

N. von Hentig[1], C. Koenigs[2], S. Elanjikal[2], R. Linde[2], D. Dunsch[2], W. Kreuz[2], M. B. Funk[2]

[1]Institute for Clinical Pharmacology at the Johann Wolfgang Goethe University, Frankfurt, Germany
[2]Children´s Hospital, Johann Wolfgang Goethe University Frankfurt, Germany

Abstract
Background: International guidelines for the treatment of HIV-1 infected children recommend efavirenz plus nucleoside reverse transcriptase inhibitor combination therapy for first line therapy. Until now little is known about the steady state pharmacokinetics of efavirenz in children.
Methods: 11 HIV-1 infected children at the age of 4 to 10 years received efavirenz according to body weight adjusted dose recommendations at 10 -15mg/kg body weight. All children were non nucleoside reverse transcriptase inhibitor (NNRTI) naïve, 5/11 received efavirenz as first line therapy. Efavirenz plasma concentrations were assessed before daily dose and 1, 2, 4, 8, 24 h post-dose after medication by established HPLC.
Results: 7 of 11 children exhibited efavirenz plasma concentrations below targeted ranges. Mean (95% CI) minimum concentrations (C_{min}) was 1293 ng/mL (range: 889 -1697) and maximum concentration (C_{max}) was 5552 ng/mL (3951 - 7153) and the mean area under the time-concentration curve at steady state (AUCss) was 63608 ng*h/mL (44222 - 82989). The linear regression analysis of bodyweight adjusted efavirenz AUCss showed a close correlation between dose/bodyweight and plasma concentrations (r^2 = 0.79). Efavirenz doses below 12.5 mg/kg lead to an AUC < 60000 ng*h/mL in 7 of 8 cases. Higher efavirenz doses exhibited an AUC within the recommended therapeutic range of 60000 – 120000 ng*h/mL (n = 3).
Conclusions: The data show insufficient plasma concentrations for some children despite efavirenz dosing according to recommendations. Antiretroviral therapy needs to be carefully adjusted in children. Therapeutic drug monitoring is strongly recommended to meet efavirenz plasma levels within the therapeutic range.

Key words: HIV-1, Efavirenz

INTRODUCTION

International guidelines recommend two nucleoside reverse transcriptase inhibitors (NRTI) plus a protease inhibitor (PI) or the non-nucleoside reverse transcriptase inhibitor efavirenz as first line therapy for HIV-1 infected children older than 3 years of age. Therapy guidelines for children under the age of 3 years or with a bodyweight below 13 kgs do not include any dosing recommendations [1, 2]. The clinical recommendations for the treatment of children with efavirenz are mainly based on data assessed in adult patients [3, 4]. As shown by Marzolini et al. [5] in adult patients on once-daily dosing, optimalefavirenz plasma concentrations range between 1000 and 4000 ng/mL. Brundage et al. [6] demonstrated a significantly higher risk of viral rebound in children exhibiting low efavirenz concentrations compared to children with sufficient plasma concentrations without defining a therapeutic range.

Efavirenz therapy regimens in children base on a bodyweight adjusted dosing of 10.0-16.7 mg/kg. In 48 pediatric patients receiving the equivalent of a 600mg dose of efavirenz in combination with nelfinavir, mean (± SD) efavirenz steady state AUC (AUCss) was 218 ± 104 μM*h [ACTG 382, sustiva® product information] and the target range was defined as 190 to 380 μM/L by Starr et al. [8] which is equivalent to 68818 (± 32831) ng*h/mL and 59979 - 119958 ng/mL.

Several studies described a good clinical benefit in children receiving a highly active antiretroviral therapy containing efavirenz. Fraaij (2004) and Bergshoeff (2005) refer to results of a clinical trial evaluating a combination of efavirenz plus lopinavir/ritonavir without NRTI, showing favourable clinical results and describing the need of a dose escalation of the combination partner lopinavir/ritonavir due to cytochrome-induced drug-drug interactions [9,10]. Puthanakit et al. (2005) recently described good virological and clinical results of the first line therapy with NRTI plus efavirenz in 107 Thai children. After 72 weeks of therapy, 76% of the patients exhibited viral loads below 50 copies/mL and an increase in CD4 cell percentage of 18% [11]. Mainly transient central nervous or cutaneous side effects were reported in the observational study of Teglas et al in 42% of the treated children, leading to a withdrawal from therapy in 21% of these cases [12]. CNS symptoms such as abnormal dreams were reported in patients with high peak plasma efavirenz levels [13].

Until today there is still limited pharmacokinetic experience with efavirenz in children when combined

with NRTI only. We therefore investigated the steady state pharmacokinetics of such a combination in pediatric patients from 4 to 12 years of age.

Patients and Methods

Patients

11 perinatally infected children (4 male/ 7 female) were treated with efavirenz plus two NRTI in an open prospective study for previously NNRTI naïve children over a period of 24 months. Study design was approved by the local ethics committee. Antiretroviral therapy was started when the children entered category B or 2 of the HIV infection according North American or German pediatric guidelines [1, 14]. Patient baseline characteristics are described in Table 1. All patients received efavirenz plus two NRTI. Efavirenz and the NRTIs were dosed according to recommendations given by international HIV treatment guidelines and manufacturers. Because efavirenz suspension was not tolerated capsules were given to all children even to infants (age < 5 years). Clinical benefit, course of viral load and CD4 cell count, as well as adverse effects and compliance of the majority of our children on a first line therapy with efavirenz were published recently and therefore not mentioned in this paper [13].

Table 1. Baseline characteristics of 11 paediatric patients.

parameter	median	range
male / female	4 / 7	
age (years)	8.7	4.3 - 12.0
weight (kg)	25.0	16.0 - 50.0
height (cm)	128.8	108.5 - 164.0
bodysurface (m^2)	1.01	0.72 - 1.51
CD4 (cells/µl)	704	398 -1550
CD4 (%)	33.0	29.9 - 42.6
VL log 10 copies/ ml	3.76	1.28 - 5.65
Concomitant NRTIs		n =
	Didanosine	7
	Lamivudine	5
	Stavudine	5
	Zidovudine	4
	Abacavir	1

Pharmacokinetic Assessment

On the day of the pharmacokinetic assessment fasting trough levels were obtained immediately before drug intake, followed by breakfast. Plasma samples were then collected at 1; 2; 4; 8; 24 hours after the drug intake, while patients remained in-houseand comedication was documented. None of the patients received concomitant medication known to interact with efavirenz at the cytochrome P450 metabolism.

Plasma drug concentrations were measured by validated high performance liquid chromatography-tandem mass spectrometry (Laboratory Prof. M. Kurowski, Berlin, Germany) according a previously described method [15].

Pharmacokinetic Evaluation

Pharmacokinetic calculations based on plasma concentrations which were above the lower limit of quantification (LLQ). The pharmacokinetic parameters were calculated according to a non-compartmental approach. The C_{min} respectively C_{max} values at the non-compartmental analysis were read directly from the plasma concentration-time curves of efavirenz within the standard dosing interval (τ = 24 hours) The following pharmacokinetic parameters were obtained by using a non-compartmental analysis model: AUC (τ) = AUCss (0.24) is the area under the concentration-time curve at steady state conditions from time zero (trough) over the time span of the dosing interval t = 24h, obtained with the logarithmic trapezoidal rule. The total clearance of efavirenz was determined by CL_{tot} = D/AUC(τ) assuming complete bioavailability. The steady state half-life ($t_{1/2}$) was calculated from the elimination constant λz with the equation:

$$t_{1/2} = \frac{\ln^2}{\lambda_z} \text{ (time)}.$$

Plasma concentration values of the last 3 time points were weighted equally. The volume of distribution following oral administration of the drugs was calculated by $V_z = CL/\lambda_z$ (L). All pharmacokinetic analyses were performed with WinNonLin™, distributed by Pharsight Corporation, Mountainview, USA [16].

Statistical Methods

Pharmacokinetic parameters were subject to descriptive statistics (mean, 95% CI). Primary target variables were the AUC_{SS} (τ), C_{max}, C_{min}, CLtot, and t1/2 of efavirenz. Normal distribution of values was determined for each time point and group according to the Kolmogoroff-Smirnoff-Liljefors test prior to the statistical analyses of parameters.

A linear regression analysis described the effect of weight-related efavirenz dosing on the area under the time-concentration curve of efavirenz at steady state. A 95%-confidence interval was calculated from the real and simulated data for efavirenz doses of 10, 11, 12, 13, 14, 15, 16 and 17mg/kg bodyweight. Descriptive statistical analysis used SPSS 11.5 for Windows [17] and the Pearson linear regression analysis of the dose/bodyweight-dependent plasma exposure was performed with Graphpad Prism 4.01 [18].

Results

Patients Disposition

4 male and 7 female patients were investigated. As shown in Table 1 the median age was 8.7 years (range: 4.3 - 12.0) at the time of the pharmacokinetic assess-

ment. The weight ranged between 16 and 50 kg (median: 25), height ranged between 108.5 and 164 cm (median: 128.8) and bodysurface between 0.72 and 1.51 m^2 (median: 1.01). The time from treatment onset to the pharmacokinetic investigation varied from 8 to 92 weeks (median: 127). Baseline median CD4-cell count was 597 cells per µl (range: 58 – 820) and median viral load was 3.76 (range: 1.28 - 5.65) log10 copies/ml.

Pharmacokinetics

The children exhibited pharmacokinetic parameter values as described in Figure 1: The mean (95%CI) AUCss was 63608 ng*h/mL (44222 - 82989). Mean C_{min} and C_{max} were 1293 ng/mL (889 -1697) and 5552 ng/mL (3951 - 7153). Mean (95%CI) clearance, half-life and volume of distribution were 97 mL/min (73 - 121), 12.93 hrs (11.4 - 14.46) and 100.5 l (58 - 142) respectively. The median efavirenz dose was 12.3 mg/kg bodyweight within a range of 10.1 -15.6 mg/kg. 7 of 11 children exhibited an AUC < 60000ng*h/mL, which is shown in Figure 2. A linear regression model showed a close correlation between efavirenz dose/bodyweight and plasma concentration ($r^2 = 0.79$).

Discussion

As shown by Marzolini et al. in adult patients dosed once daily, optimum plasma efavirenz levels ranged from 1000 to 4000ng/mL [5]. Virological failure has been observed in 50% of the studied patients with efavirenz levels below 1000 µg/l and CNS toxicity was approximately three times more frequent in patients with efavirenz levels > 4000 ng/mL. Brundage et al. analysed pharmacokinetic data of the PACTG study 382 and found a significantly higher rate of children failing therapy, if the efavirenz AUC was lower than 190 µM*h/L or > 59979 ng*h/mL respectively at week 6 [6].

Although the children of our study were dosed according to international guidelines adjusting efavirenz dosage to bodyweight, the majority of detected efavirenz levels did not reach recommended target values: 7/8 children with a bodyweight greater than 35 kg

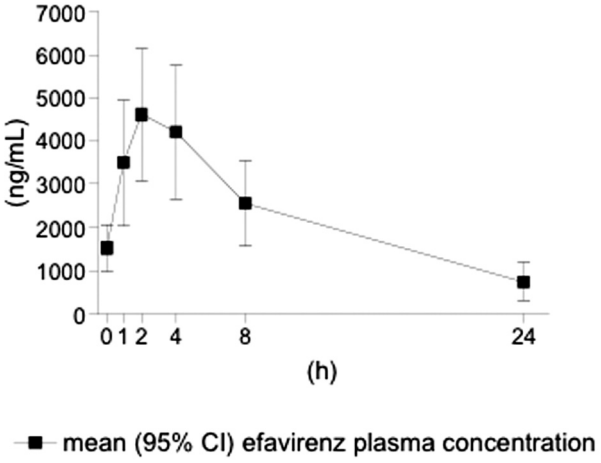

Fig. 1. Efavirenz plasma time-concentration curve over the dosing interval.

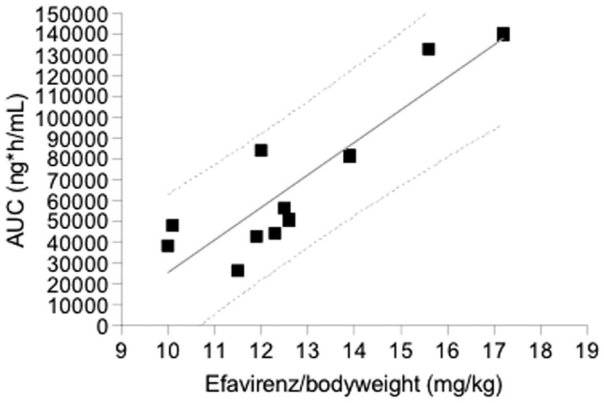

Fig. 2. Linear regression of bodyweight-adjusted efavirenz AUCss: Mean and 95%-confidence interval; $r^2 = 0.79$.

Table 2. 95%-confidence intervals of the mean AUCss/dose according to the Pearson linear regression test.

Efavirenz dose/bodyweight (mg/kg)	Mean Efavirenz AUCss (ng*h/mL)	95 % - Confidence Interval of the AUCss [1] (ng*h/mL)
10	25773	5286 – 46260
11	41390	25270 – 57510
12	57015	43860 – 70170
13	72640	60030 – 85250 2
14	88245	73490 – 103000 2
15	103885	85170 – 122600 2
16	119475	95950 – 143000
17	135150	106300 – 164000
18	150650	116300 – 185000

[1] Y-intercept if X = mg/kg
[2] Values within recommended range of efavirenz AUCss: 60000 - 120000 ng*h/mL

and a dose of less than 12.5 mg efavirenz per kg bodyweight exhibited an efavirenz AUCss of less than 60000 ng*h/mL. The close correlation between bodyweight, dosage and plasma concentrations of efavirenz was underlined by the regression model.

Starr et al. [19] reported that 22 of 50 paediatric patients (44%) with a mean efavirenz dose of 11.7 mg/kg/d exhibited insufficient plasma levels (< 190 μM*h/L) at week 2. Therefore the average dose of evafirenz was increased up to 14.2 mg/kg/d. In a further study with younger children who received a mean efavirenz dose of 15.7 mg/kg/day as liquid formulation, in 11 of 18 patients (61%) an AUC of < 190 μM*h/L was detected, and doses were also increased in the affected patients. These data support our findings, that efavirenz could be under-dosed in a considerable number of pediatric patients.

According to the linear regression model (results are shown in Table 2 and Figure 2) children with >35kg bodyweight show a tendency towards efvavirenz plasma concentrations being lower than the recommended AUC of 60.000 ng*h/mL. Taking into account that patients also exhibit a considerable intraindividual variability of efavirenz plasma drug levels [20] it seems to be recommendable to adjust the dose continuously to increasing weight until the adult dose of 600mg is reached in order to keep it within the warranted plasma concentration ranges.

As the number of investigated children is small, it is not suitable to draw any final conclusions. But we have to focus on the special pharmacokinetics of children treated with efavirenz and therefore at least recommend TDM according to a standardized protocol. This enables clinicians to adjust dosage after study onset in order to reach values of an AUC of 60.000 – 120.000 ng*h/mL and therapeutic plasma concentrations of 1000 - 4000 ng/mL over the dosing interval. Additional information about pharmacokinetics of HAART in children should be added to the current therapeutic knowledge.

REFERENCES

1. http://AIDSinfo.nih.gov. Guidelines for the use of antiretroviral agents in pediatric HIV infection. 2005.
2. Sharland M, Blanche S, Castelli G, et al. on behalf of the PENTA Steering Committee. PENTA guidelines for the use of antiretroviral therapy 2004. HIV Med 2004,5:61-86.
3. Staszewski S, Moralez-Ramirez J, Tashima KT, et al. Study 006- Team. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. N Engl J Med. 1999, 341: 1865-1873.
4. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. Lancet 2004, 363: 1253-1263.
5. Marzolini C, Telenti A, Decosterda LA, et al. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. AIDS 2001,15:71-75.
6. Brundage RC, Yong FH, Fenton T, et al. Intrapatient variability of efavirenz concentrations as a predictor of virologic response to antiretroviral therapy. Antimicrob Agents Chemother. 2004, 48: 979-984.
7. BristolMyersSquibb. Sustiva product information. Apr 2005. T4-B0001-04-05/Revised. princeton, NJ08543, USA. http://www.bms.com/products/data/index.html
8. Starr SE, Fletcher CV, Spector SA, et al.; PACTG 382 Study Team. Pediatric AIDS Clinical Trials Group. Efavirenz liquid formulation in human immunodeficiency virus-infected children. Pediatr Infect Dis J 2002, 21:659-663.
9. Fraaij PL, Neubert J, Bergshoeff AS, et al. Safety and efficacy of a NRTI-sparing HAART regimen of efavirenz and lopinavir/ritonavir in HIV-1-infected children. Antivir Ther 2004, 9:297-299.
10. Bergshoeff AS, Fraaij PL, Ndagijimana J, et al.. Increased dose of lopinavir/ritonavir compensates for efavirenz-induced drug-drug interaction in HIV-1-infected children. J Acquir Immune Defic Syndr. 2005; 39(1): 63-8
11. Puthanakit T, Oberdorfer A, Akarathum N, et al. Efficacy of highly active antiretroviral therapy in HIV-infected children participating in Thailand's National Access to Antiretroviral Program. Clin Infect Dis 2005,41:100-107.
12. Teglas JP, Quartier P, Treluyer JM, et al. Tolerance of efavirenz in children. AIDS 2001, 15: 241-243.
13. Funk MB, Notheis G, Schuster T, et al. Effect of first line therapy including efavirenz and two nucleoside reverse transcriptase inhibitors in HIV-infected children. Eur J Med Res 2005,10:503-508.
14. Niehues T, Wintergerst U, Funk MB, et al. Empfehlung zur antireroviralen Therapie bei HIV-infizierten Kinder - Konsensusstatement der Pädiatrische Arbeitsgruppe AIDS (PAAD) (german). Monatsschr Kinderheilk 2001,149:1372 - 1382.
15. Marzolini C, Telenti A, Buclin T, et al. Simultaneous determination of the HIV protease inhibitors indinavir, amprenavir, saquinavir, ritonavir, nelfinavir and the non-nucleoside reverse transcriptase inhibitor efavirenz by high-performance liquid chromatography after solid-phase extraction. J Chromatogr B Biomed Sci Appl. 2000, 740: 43-58.
16. WinNonLin®. Version distributed by Pharsight Corporation, USA. 2004.
17. SPSS für Windows®. Version 11.5 (deutsch) 2004.
18. GraphPadPrism®. Version (deutsch). 2004,4.01.
19. Starr SE, Fletscher CV, Spector SA., et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. N Engl J Med. 1999 Dec 16; 341(25):1874-81.
20. Nettles R, Kieffer T, Parsons T, et al. Frequent sampling in virologically suppressed patients taking HIV protease inhibitors of non-nucleoside reverse transcriptase inhibitors defines intra-individual pharmacokinetic variability. In: 12th Conference on Retroviruses and opportunistic Infections, Boston, USA 2005, Abstract 642.

Received: May 15, 2006 / Accepted: June 30, 2006

Adress for correspondence:
Dr. med. Nils von Hentig
Institute for Clinical Pharmacology
pharmazentrum frankfurt/ZAFES
J.W. Goethe University Hospital
Theodor-Stern-Kai 7
D-60590 Frankfurt am Main
Germany
Phone: +49-69-63016956
Fax: +49-69-63017636
Email: Hentig@em.uni-frankfurt.de