Antiviral efficacy, tolerability and pharmacokinetics of efavirenz in an unselected cohort of HIV-infected children

U. Wintergerst¹, F. Hoffmann¹, A. Jansson¹, G. Notheis¹, K. Huß¹, M. Kurowski² and D. Burger³*

¹Department of Immunodeficiency Diseases, Children’s Hospital of the Ludwig Maximilians University, Munich, Germany; ²HIV Laboratory Therapia GmbH, Immunologisches Tagesklinik, Berlin, Germany; ³Department of Clinical Pharmacy, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

Received 4 November 2007; returned 11 December 2007; revised 26 January 2008; accepted 18 February 2008

Introduction

The non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz is licensed for use in children aged 3 years and older by both European and US regulatory authorities.¹,² Data on paediatric use of efavirenz that led to approval were obtained from the PACTG 382 study,³ in which NRTI-pre-treated subjects received efavirenz in combination with nelfinavir and one or two NRTIs.

Almost 10 years after the publication of the PACTG 382 study, a few comments can now be made on the use of efavirenz in routine clinical paediatric practice. Firstly, nowadays, children usually start with efavirenz without being previously treated with mono- or dual therapy with NRTIs, and a combination of efavirenz with nelfinavir is not a recommended regimen for a treatment-naive child according to the most recent treatment guidelines.⁴,⁵ Secondly, virological efficacy and tolerability may differ between clinical trials such as PACTG 382 and routine clinical patient care. Thirdly, only a few studies have been conducted that have prospectively validated the adjusted dosing table (mean efavirenz dose: 15 mg/kg body weight once daily) in treatment-naive HIV-infected children with respect to target plasma drug concentrations, viral load response and tolerability.⁶–¹⁰ In two of these studies,⁸,¹⁰ a high prevalence of subtherapeutic plasma concentrations of efavirenz was noted (63.6% and

Keywords: non-nucleoside reverse transcriptase inhibitor, paediatrics, therapeutic drug monitoring

Methods: To obtain data on the pharmacokinetics of efavirenz in children in clinical practice.

Results: Thirty-three children were included. Median (range) age, body weight, dose and dose/kg were 8.2 (2.1–16.7) years, 24 (12–62) kg, 300 (200–800) mg and 13.3 (9.7–22.5) mg/kg, respectively. Median (range) efavirenz plasma concentration at first sampling was 2.8 (0.13–11.6) mg/L. Plasma concentrations were not dependent on age (P = 0.97) or dose/kg (P = 0.87). A total of 307 efavirenz plasma concentrations were determined. Forty-five samples (14.7%) contained >4.0 mg/L, and 27 samples (8.8%) contained <1.0 mg/L. Eight children (24%) reported persistent adverse events probably caused by efavirenz [concentration problems (5), sleep disorder (1), psychotic reaction (1) and seizure (1)]; six discontinued efavirenz for this reason. A non-significant trend existed towards a higher proportion of toxic efavirenz plasma concentrations (>4.0 mg/L) in subjects who reported efavirenz adverse events: 25.9% versus 12.8% (P = 0.23; t-test). Viral load was <50 copies/mL in all 27 subjects who continued efavirenz, despite occasional subtherapeutic efavirenz plasma concentrations in 12 children. The occasional subtherapeutic levels suggest that temporal non-adherence was present.

Conclusions: Efavirenz as part of highly active antiretroviral therapy was highly effective in children able to tolerate the drug. Therapeutic drug monitoring (TDM) as part of toxicity management may prevent discontinuation in a subset of patients. Temporal non-adherence occurs frequently. TDM may allow initiation of adherence interventions before viral load becomes detectable.

Keywords: non-nucleoside reverse transcriptase inhibitor, paediatrics, therapeutic drug monitoring

*Correspondence address. Department of Clinical Pharmacy, 864 Radboud University Nijmegen Medical Centre, Geert Grooteplein 10, 6525 GA Nijmegen, The Netherlands. Tel: +31-24-3616405; Fax: +31-24-3668755; E-mail: d.burger@akf.umcn.nl

© The Author 2008. Published by Oxford University Press on behalf of the British Society for Antimicrobial Chemotherapy. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org
Efavirenz pharmacokinetics in children

Methods

The Department of Immunodeficiency Diseases at the Ludwig Maximilian University Children’s Hospital takes care of a cohort of 75 HIV-infected children in the Bavarian region. At every routine visit, blood is sampled for plasma efavirenz concentration, viral load, CD4 count and clinical chemistry/haematology. Time between dose and blood sampling was assessed by parental report. Here, we report on all children started on efavirenz since 2000.

Efavirenz was dosed on body weight according to the dosing table in the product information (Table 1). Only efavirenz capsules and tablets were used; no liquid formulation was used because of its poor bioequivalence with the solid dose formulations and the poor acceptability by the children.

Plasma efavirenz concentrations were determined at HIV Laboratoria Therapia GmbH, Berlin, Germany, using a validated HPLC method with UV detection. The method is validated for a calibration range of 0.078–10.0 mg/L. The therapeutic range of random efavirenz plasma concentrations was defined as 1.0–4.0 mg/L, based on an international consensus document. Apparent efavirenz plasma clearance, corrected for body weight (CL/F·kg), was calculated as dose (in mg/kg)/[Cₚ (in mg/L)×dose interval (24 h)]. When more than one efavirenz plasma concentration was available, the geometric mean clearance was calculated. A successful antiviral response was defined as a viral load below the detection limit of 50 copies/mL. A virological ‘blip’ was defined as a viral load measurement between 50 and 1000 copies/mL preceded and followed by repeated measurements below 50 copies/mL. Statistical analyses were performed using SPSS version 14.0.

Results

A total of 33 children were included between January 2000 and September 2005. Twenty-eight children were treatment-naive at the time of the first efavirenz measurement and two NRTIs; the remaining five children were pre-treated with NRTIs and received combinations of efavirenz, NRTIs and a protease inhibitor. Median (range) age, body weight and efavirenz dose (in mg and mg/kg) at the time of the first efavirenz measurement were 8.2 (2.1–16.7) years, 24 (12–62) kg, 300 (200–800) mg and 13.3 (9.7–22.5) mg/kg, respectively. There were 24 Caucasians, 7 Africans and 2 Asian children. Median (+range) efavirenz plasma concentration at first sample was 2.8 (0.13–11.6) mg/L. The efavirenz plasma concentration in this sample was not dependent on age (P = 0.97) or dose/kg (P = 0.87).

Median (range) duration of follow-up on efavirenz was 50 (2–81) months, during which a median (range) of 10 (2–25) samples for therapeutic drug monitoring (TDM) were taken. There were a total of 307 TDM samples evaluable for analysis. Almost two-thirds of the samples (199/307, 64.8%) were taken between 8 and 20 h after the last intake. Of 307 samples routinely taken for TDM of efavirenz, 72 (23.5%) were outside the therapeutic range (1.0–4.0 mg/L). The median (range) apparent efavirenz plasma clearance was 0.30 (0.07–1.0) L/h·kg in this cohort of 33 children. There was a significant and inverse relationship between efavirenz clearance and age (Figure 1), although the correlation coefficient was only 0.1813, indicating that only a small part of interpatient variability in efavirenz clearance was explained by age.

There were eight children who presented with persistent CNS symptoms that were possibly or probably related to efavirenz: five had concentration problems; other complaints were sleep disorders, psychotic reaction and seizure (n = 1 each). Six of these children (18.2% of the cohort) had to discontinue efavirenz because of these adverse events; the reported symptoms disappeared after switching to nevirapine or a boosted protease inhibitor. A total of 45 samples (14.7%) contained an efavirenz concentration higher than 4.0 mg/L. These came from a total of 14 children (42.4% of the cohort) who had at least one sample >4.0 mg/L. There was a non-significant trend of a higher proportion of toxic efavirenz plasma concentrations in children who reported adverse events versus those who did not report adverse events: 25.9% versus 12.8% (independent samples t-test; P = 0.23).

Twenty-seven children were able to tolerate efavirenz and were analysed for antiviral response: all children had a viral load of <50 copies/mL at the end of follow-up. Including the six children who discontinued efavirenz because of adverse events, this makes a response rate of 81.1% according to an intention-to-treat approach, non-completer equals failure (NC = F). There were a total of 27 samples (8.8%) that contained an efavirenz concentration below 1.0 mg/L. These 27 samples came from 12 children (36.4% of the cohort) who had at least one sample <1.0 mg/L. Although these 12 children all had an undetectable viral load at the end of follow-up (discussed earlier), in 4 of them blips were observed (33.3%). This incidence of blips was non-significantly lower in the remaining

Table 1. Dosing table for efavirenz as recommended by the manufacturer

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Efavirenz dose (mg), once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 to &lt;15</td>
<td>200</td>
</tr>
<tr>
<td>15 to &lt;20</td>
<td>250</td>
</tr>
<tr>
<td>20 to &lt;25</td>
<td>300</td>
</tr>
<tr>
<td>25 to &lt;32.5</td>
<td>350</td>
</tr>
<tr>
<td>32.5 to &lt;40</td>
<td>400</td>
</tr>
<tr>
<td>&gt;40</td>
<td>600</td>
</tr>
</tbody>
</table>

Figure 1. Apparent efavirenz (EFV) clearance versus age. The regression equation is: \( CL = 0.513 - \text{age (years)} 	imes 0.023; R^2: 0.183; F = 6.715 \) and \( P = 0.015 \).

40.0%, respectively). Therefore, there is an urgent need for more prospectively collected data on the use of efavirenz in HIV-infected children.
21 children without an efavirenz concentration of <1.0 mg/L (19.0%; P = 0.36).

Discussion

This unselected cohort of HIV-infected children attending a university outpatient clinic in Munich, Germany, with a median duration of follow-up of more than 4 years, showed an excellent antiviral response (on treatment: 100% and NC = F: 81.1%) and a relatively low discontinuation rate of 18.2%. Non-significant trends were observed for higher plasma concentrations of efavirenz in children who suffered from CNS-related adverse events and for a higher incidence of viral load blips in children with subtherapeutic efavirenz plasma concentrations.

The antiviral response in this cohort of 33 children is higher than previously observed in the PACTG 382 study: 81% versus 53%. The most likely explanation is the low proportion of children who had been pre-treated with mono- or dual therapy with NRTIs at our institution in comparison with the study population of PACTG 382. In PACTG 382, pre-treatment with NRTIs was an inclusion criterion, reflecting the treatment options at the end of the last century for HIV-infected children. In contrast, median duration of follow-up was 50 months in our cohort, which is almost four times longer than the 48 weeks as reported by PACTG 382.

Wintergerst et al. 8

Our cohort is better to compare with a Dutch cohort followed at the Academic Medical Center (AMC) in Amsterdam; 9 36 children were followed around the same period as our cohort and only 10 were NRTI-pre-treated. The virological failure-free survival in their cohort was 76% and 67% after 48 and 96 weeks, respectively, which indicates a somewhat lower response than we describe. A smaller cohort of 10 children treated in Frankfurt, Germany, reported 80% virological response after 24 months of treatment. 7 The UK CHIPS cohort published a 79% virological response (viral load <400 copies/mL) after 12 months of treatment in children initiating highly active antiretroviral therapy regimens between 2003 and 2006, 13 but this also includes non-efavirenz-based regimens. A recent PACTG study (P1021) investigated a once-daily regimen of efavirenz, emtricitabine and didanosine in 37 treatment-naive children and found a 72% response rate (viral load <50 copies/mL) at week 96. 14 Differences in study population, sample size, selected doses and treatments, duration of follow-up and so on could be an explanation for variability in treatment outcomes among cohorts.

The discontinuation rate of efavirenz in our cohort was 18.2% (6/33), which is comparable with the values found in PACTG 382 (14/55, 24.6%) and P1021 (11/37, 29.7%) and somewhat lower than in the AMC cohort (14/36, 38.9%). It is encouraging to see that discontinuation rates of efavirenz-containing regimens in children are similar to or lower than those observed in clinical trials. Usually, in clinical practice, it is more difficult to motivate patients to continue on treatment than in clinical trials, but our data suggest a best-practice approach in which management of adverse events is optimized in order to reduce treatment changes as much as possible. The most frequently observed efavirenz-related adverse event in our cohort was concentration problems, which is, in particular, problematic for children attending school. In some cases, the persistence of CNS-related adverse events may be caused by toxic or supratherapeutic efavirenz plasma concentrations (i.e. >4.0 mg/L 11) and, here dose reductions guided by TDM may prevent discontinuation of an otherwise effective antiretroviral agent.

The proportion of TDM samples outside the therapeutic range (23.5%) is very similar to the value observed in a cohort of 255 adult patients in the Netherlands, in which a random TDM sample was taken (36/255, 22%). 13 The most likely explanations for an efavirenz plasma concentration outside the therapeutic range are non-adherence, drug–drug interactions, genetic influences (CYP2B6 polymorphism 16) and so on. In children, suboptimal dosing could be a specific reason causing a non-therapeutic efavirenz plasma concentration and here TDM may play a role in optimizing efavirenz-based regimens. TDM is also useful in detecting temporary non-adherence, as indicated by a relatively high proportion of children with at least one virological blip, despite prolonged antiviral response (8/33, 24%).

Recently, two independent papers have presented a high proportion of children with subtherapeutic plasma concentrations of efavirenz. von Hentig et al. 8 reported that 7 of 11 children had a subtherapeutic AUC despite dosing according to the recommendations. The second paper is from Ren et al. 10 who describe efavirenz plasma concentrations in 15 HIV-infected South African children. The estimated efavirenz concentration at 24 h was below 1.0 mg/L in six of them (40%), and there was an association with a higher likelihood of detectable viral load in these children with subtherapeutic plasma concentrations of efavirenz. It has been predicted that efavirenz plasma concentrations would have been higher in African patients when compared with Caucasians, due to a higher proportion of patients with a genetic polymorphism in CYP2B6, the principal enzyme responsible for efavirenz metabolism. 17 The data from the small study of Ren et al. indicate that genetics is only one factor influencing efavirenz pharmacokinetics and that other factors are also (or even more) important.

In conclusion, we describe the largest clinical cohort of HIV-infected children reported so far, having a relatively low discontinuation rate and 100% virological response in children who are able to tolerate efavirenz. TDM may be indicated to detect efavirenz plasma concentrations outside the therapeutic range to detect incorrect dosing and/or temporary non-adherence; in addition, it can be a helpful tool in toxicity management.

Funding

No specific funding was received for this study.

Transparency declarations

None to declare.

References


3. Starr SE, Fletcher CV, Spector SA et al. Combination therapy with efavirenz, nevirapine, and nucleoside reverse-transcriptase
Efavirenz pharmacokinetics in children

inhibitors in children infected with human immunodeficiency virus type


