Changes in indinavir exposure over time: a case study in six HIV-1-infected children

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Objective: To study changes in indinavir exposure over time in HIV-1-infected children.

Materials and methods: Protease inhibitor (PI)-naive HIV-1-infected children were treated with indinavir, zidovudine and lamivudine. Steady-state plasma pharmacokinetic (PK) sampling was carried out as standard of care. The AUC₀–₈ was targeted between 15 and 30 mg·h/L. PK sampling was repeated after dosage adjustment until the AUC₀–₈ reached target values. Patients were included when the time interval between PK samplings was ≥2 years and differences in dosage/m² < 10% between PK samplings 1 and 2. Corrections of dose for changes in body size were carried out.

Results: Six children were enrolled with a median age of 5.2 years (range 1.7–13.6 years). All had a viral load below 500 copies/mL. The geometric mean (GM) of the AUC₀–₈ decreased from 25.3 mg·h/L at the first PK-day to 19.1 mg·h/L at the second PK-day [geometric mean ratio (GMR): 0.76 (95% C.I.: 0.48–1.20)]. The GM of Cₘₐₓ decreased from 11.8 to 10.4 mg/L [GMR: 0.88 (95% C.I.: 0.59–1.32)]. The GM of Cₘᵋᵢₙ decreased from 0.08 to 0.07 mg/L [GMR: 0.86 (95% C.I.: 0.62–1.18)]. All children had an AUC₀–₈ above 15 mg·h/L on the first PK-day; three had an AUC₀–₈ below 15 mg·h/L on the second PK-day. In two of these three children, the plasma viral load was >500 copies/mL.

Conclusion: Changes in indinavir exposure were observed over time. In two patients, decreased indinavir exposure was associated with virological failure. Therapeutic drug monitoring should be carried out over time since this may prevent subtherapeutic dosing in children.

Keywords: pharmacokinetic analysis, age, development, paediatric HIV/AIDS, pharmacokinetics, protease inhibitors, indinavir

Introduction

Since the introduction of highly active antiretroviral therapy (HAART), the life expectancy of HIV-1-infected children has improved dramatically.¹ Still, institution of optimal treatment poses a major challenge. In children, large inter-individual differences are observed in the pharmacokinetics of antiretroviral drugs, especially in protease inhibitors (PI). For example Burger et al. showed 18-fold variability (2.8–51 mg·h/L) in the AUC₀–₈ of indinavir in children treated with a dosage of 33 mg/kg metabolic weight.² This is even more important when one considers that the level of viral suppression and the plasma concentration of indinavir are associated in adults and children.³⁴ Therefore, we routinely carry out pharmacokinetic analysis of plasma concentrations of PI in our hospital. Our approach has resulted in favourable results with 69% viral response after 2 years of treatment.¹ Yet, viral failure occurs in some of the children. Data in animals and adults indicate that exposure to PI may gradually decrease over time.⁵ Currently there is no information on changes in the pharmacokinetic parameters after prolonged PI use in children. However, changes over time can be expected in children, since the processes of growth and development have a significant impact on drug absorption, distribution and clearance.⁶ Decreased drug exposure over time may lead to viral rebound, selection of resistant mutants and ultimately to treatment failure. We present here a case study on the effects of time on indinavir exposure in six HIV-1 over infected children.

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Materials and methods

Patients

PI-naive HIV-1-infected children with a viral load above 5000 copies/mL and/or a CD4 cell count below their age-specific reference value started HAART consisting of indinavir 400 mg/m² every 8 h, zidovudine 120 mg/m² every 8 h and lamivudine 4 mg/kg every 12 h. In all patients, steady-state intensive plasma PK sampling of indinavir was carried out as standard of care. The AUC₀–₈ was targeted between 15 and 30 mg h/L². PK sampling was repeated until the AUC₀–₈ reached target values. Hereafter, PK sampling was not routinely repeated. However, in case of viral failure, single sample indinavir plasma levels were considered. Children were eligible for inclusion in this study when data were available from both the first intensive PK sampling with the dose resulting in an adequate AUC₀–₈ (=PK-day 1), and second intensive pharmacokinetic sampling (=PK-day 2) on this (fixed) dose/m², with a minimum interval of 2 years. Dose adjustments < 10% of dosage in mg/m² body surface area (BSA) were allowed between PK samplings. Corrections of dose for changes in body size were carried out for indinavir and for nucleoside analogues. Changes in body size were calculated in plasma by HPLC, as previously described. AUC₀–₈ concentrations were determined in plasma by HPLC, and samples were stored at °C until analysis. Indinavir concentrations were determined in plasma by HPLC. Plasma was separated by centrifugation (10 min at 3000g) and samples were stored at –20°C until analysis. Indinavir concentrations were determined in plasma by HPLC. Plasma was separated by centrifugation (10 min at 3000g) and samples were stored at –20°C until analysis. Indinavir concentrations were determined in plasma by HPLC. Plasma was separated by centrifugation (10 min at 3000g) and samples were stored at –20°C until analysis. Indinavir concentrations were determined in plasma by HPLC. Plasma was separated by centrifugation (10 min at 3000g) and samples were stored at –20°C until analysis.

Pharmacokinetics

Patients took indinavir on an empty stomach and blood samples were collected at time points 0 (pre-dose) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7 and 8 h post-ingestion. Plasma was separated by centrifugation (10 min at 3000g) and samples were stored at –20°C until analysis. Indinavir concentrations were determined in plasma by HPLC. Plasma was separated by centrifugation (10 min at 3000g) and samples were stored at –20°C until analysis.

Results

Between 1997 and 2001, 35 children started indinavir every 8 h in our hospital. The children had a median age of 3.2 years (range 0.2–13.6 year). Fifty-four percent of the patients were female. Sixty-three percent of the children had a least one parent originating from a sub-Saharan country (n = 22). At the time of this study (2000–2001), eight children were still eligible for enrolment. Reasons not to include the remaining 27 patients in this study were: loss to follow up (n = 5), a change in indinavir dosage per m² > 10% (n = 1) and a medication change before this study was initiated (n = 21). Patients changed medication before the study because of toxicity (n = 5), patient request (n = 1), failure to obtain acceptable PK values (n = 3), medication failure (n = 5) or medication was changed to a twice daily indinavir/ritonavir containing regimen after less than 2 years of treatment with indinavir every 8 h (n = 7). Of the eight patients that could be enrolled in the study two were not. One as a result of suspected non-compliance on PK-day 2 and the other because of difficulties with obtaining PK-data owing to autism. The median age of the six included patients was 5.2 years (range 1.7–13.6) at the first PK-day and most (n = 5) had at least one parent originating from a sub-Saharan country. The time period to obtain the optimal dosage of indinavir was 1–9 months after start of indinavir 400 mg/m² (median 6 months). The median time between the first and the second PK-day was 2.5 years (range 2.0–3.5 years). On the second PK-day, the median percentage of the original dosage per m² was 98% (range 93–109%). The absolute median dosage (mg) of indinavir increased from 350 mg (range 300–800) to 450 mg (range 400–800). Three patients used co-medication on the first PK-day (amphotericin B/ co-trimoxazole, fluconazole/co-trimoxazole and co-trimoxazole). None of the patients used co-medication on the second PK-day.

In four of the six children the AUC₀–₈ had decreased on the second PK-day. In two children, the AUC₀–₈ had increased. For data of the individual patients, see Table 1. The GM of the AUC₀–₈, Cₘₐₓ, Cₚₜₙ and t½, all decreased on the second PK-day compared with the first PK-day. The pharmacokinetic parameters for the study group are summarized in Table 2.

All children had an AUC₀–₈ above 15 mg h/L on the first PK-day. On the second PK-day, the AUC₀–₈ had decreased to below 15 mg h/L in three of the six children. These three children also had the lowest AUC₀–₈ on the first PK-day. In two of these children, virus could be detected on the second PK-day, whereas all patients had a viral load below 500 copies/mL on the first PK-day (Table 1). The median CD4 cell count as a percentage of their age-specific reference value had increased from 66% (range 43–131%) to 106% (range 51–165%). No clinically relevant abnormalities were observed in blood chemistry parameters for liver and kidney functions on PK-day 1 and PK-day 2.
Discussion

Currently, no information is available on changes in PK parameters of PI after long-term PI use in children. We therefore carried out a case study in HIV-1-infected children using indinavir for a prolonged period and observed a decrease in the AUC$_{0-8}$ between PK-day 1 and PK-day 2 in four out of six children.

The differences found between the two PK curves cannot be explained by changes in the techniques, since we used the same methodology for all PK curves. Inter-assay variability is not likely to be responsible for the observed changes in indinavir exposure, since the changes in AUC$_{0-8}$ greatly exceeded the inter-assay variance. We did not observe clinically relevant abnormalities in blood chemistry parameters. Therefore, the changes in indinavir exposure were not the result of changes in organ function because of indinavir usage. Also the co-medication used on the first PK-day was not expected to have caused a difference in PK parameters, because it does not interfere with the metabolism of indinavir.

It is unlikely that growth influenced the results, since the medication dosage was based on square metres of body surface and adjusted when length or weight had changed. Interestingly, in one child (A13), the absolute dose was not increased, and still her clearance and volume of distribution had markedly increased. Hypothetically, the decreased indinavir exposure may have been caused by a decrement in indinavir exposure with age. However, this is not expected since younger children have an increased hepatic enzymic activity compared with older children and adults. Duration of therapy per se did not seem to influence the change in indinavir exposure, since both increased and decreased exposure could be shown in four children who were on therapy for approximately the same time period (2.5 years). Still, mechanisms such as the induction of P-glycoprotein and CYP 450 levels after prolonged PI usage as also shown in vitro by Huang et al. may have resulted in the decreased indinavir exposure.

Remarkably, the three children with AUC II below the 15 mg h/L threshold were the older ones, suggesting that older children may be more prone to develop sub-therapeutic indinavir levels in time.

An alternative explanation for the observed failure of therapy after prolonged use of indinavir, may be non-compliance. Yet, in one of the children with a viral load >500 copies/mL, the C$_{max}$ corresponded with the C$_{trough}$ indicating that at least the preceding dose was taken in time. However, non-compliance obviously influences the antiviral efficacy of indinavir and may thus have influenced our findings.

Clearly, our study is limited by the small sample size of six children. Still, the included patients were representative for age and race for the patient population using indinavir in our hospital. A difference existed for sex, since all patients in the study population were female. In this study, a confounding factor may be the selection of patients with decreasing exposure to indinavir, because children with increasing exposure to indinavir are more likely to suffer from complications and to discontinue treatment before a second PK sampling can be carried out. As a result, these children would not have been included in this type of study. However, we do not expect this phenomenon to be a major confounder, since only in a small group of children was the medication changed because of toxicity.

At the time of this case study, random single indinavir plasma levels were not obtained in our hospital as part of the routine care for HIV-1-infected children. It was considered after viral failure occurred, mostly to check for compliance. Currently, in our hospital both full PK samplings for PI levels and random single sample plasma PI levels are part of the routine care for HIV-1-infected children, allowing for optimal dosing and early detection of changed exposure of PI.

In conclusion, our data indicate an effect of time on indinavir exposure in HIV-1-infected children. Both increased and decreased indinavir exposure were observed over time. Sub-therapeutic plasma levels of indinavir were found, which in two of three cases were associated with viral failure. Regular monitoring of drug levels may prevent sub-therapeutic PI dosing in children receiving HAART.

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<table>
<thead>
<tr>
<th>Parameter</th>
<th>First PK-day GM (range)</th>
<th>Second PK-day GM (range)</th>
<th>GMR II/I (range)</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{0-8}$</td>
<td>25.3 (15.4–38.7)</td>
<td>19.1 (10.2–54.3)</td>
<td>0.76 (0.46–1.4)</td>
<td>0.48–1.2</td>
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<tr>
<td>C$_{max}$</td>
<td>11.8 (8.8–17.0)</td>
<td>10.4 (6.5–21.0)</td>
<td>0.88 (0.5–1.6)</td>
<td>0.59–1.32</td>
</tr>
<tr>
<td>C$_{min}$</td>
<td>0.08 (0.04–0.21)</td>
<td>0.07 (0.04–0.15)</td>
<td>0.86 (0.71–1.5)</td>
<td>0.62–1.18</td>
</tr>
<tr>
<td>V/F</td>
<td>1.67 (0.8–2.4)</td>
<td>1.45 (0.9–2.0)</td>
<td>0.87 (0.5–1.9)</td>
<td>0.49–1.54</td>
</tr>
<tr>
<td>CL/F</td>
<td>16.3 (7.4–38.8)</td>
<td>27.4 (7.4–78.3)</td>
<td>1.67 (1.0–2.7)</td>
<td>1.13–2.48</td>
</tr>
<tr>
<td>CL/F × m$^2$</td>
<td>20.6 (13.5–28.4)</td>
<td>30.9 (11–64)</td>
<td>1.5 (0.79–4.72)</td>
<td>0.75–2.98</td>
</tr>
<tr>
<td>V/F × m$^2$</td>
<td>39.3 (12.4–100)</td>
<td>62.5 (11.7–217.4)</td>
<td>1.59 (0.5–5.2)</td>
<td>0.66–3.84</td>
</tr>
</tbody>
</table>

Table 2. Changes in pharmacokinetic parameters in time in HIV-1 infected children (n=6)

Values for the first and second PK-day are presented as geometric means (GM).
involvement of these sponsors with data collection, data analysis, the writing of this article and article submission.

References


