Pharmacokinetics, Short-term Safety and Efficacy of the Approved Once-daily Darunavir/Ritonavir Dosing Regimen in HIV-infected Children

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Abstract: In this multicenter pharmacokinetic study in HIV-infected children (6–12 years of age), we validated the approved once-daily darunavir/ritonavir dosing recommendations. The geometric mean darunavir area under the plasma concentration-time curve was 63.1 h·mg/L, substantially lower than the mean value observed in adults. However, all trough levels were adequate, and short-term virologic outcome was good. These data support the use of the darunavir/ritonavir once-daily dosing recommendations.

Key Words: children, darunavir, once-daily, pharmacokinetics, HIV

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Protease inhibitors (PIs) boosted with ritonavir are advised for first-line treatment of HIV-infected children.[1,2] Once-daily use of antiretroviral treatment is preferred because of better adherence compared with twice-daily use.[1,2] Pediatric dosing recommendations for darunavir/ritonavir once-daily have been derived from results of several pharmacokinetic studies in children.[3–5] A population pharmacokinetic model was built from these data combined with adult data.[6] Pharmacokinetic data of once-daily darunavir/ritonavir for children 6–12 years of age were not available and thus not included in the model. The aim of this study was to validate current once-daily dosing recommendations for darunavir/ritonavir in children 6–12 years of age and to investigate whether exposure is comparable to the exposure in adults.

METHODS

A multicenter, open-label, pharmacokinetic study was performed in HIV-infected children using darunavir/ritonavir once-daily as part of their antiretroviral treatment. Written informed consent was obtained from the parents and assent from the child. The study was conducted in pediatric HIV centers in the Netherlands and was approved by the medical ethical committee Commissie Mensgebonden Onderzoek (CMO) Arnhem-Nijmegen; NCT02285478).

Population and Treatment

Children (6–12 years of age) were eligible when they used darunavir/ritonavir once-daily for at least 2 weeks according to the approved dose. Though not recommended in pediatric guidelines, children had been switched to darunavir/ritonavir because of clinical considerations. Other inclusion criteria were HIV-RNA <50 copies/mL for at least 6 months, a bodyweight of at least 15 kg and the ability to swallow intact tablets.

Exclusion criteria were previous failure on a PI-containing regimen, use of concomitant drugs other than the antiretroviral regimen (unless permitted by the trial team), inability to understand the nature and extent of the trial procedures, documented sensitivity to darunavir or ritonavir medicinal products or its excipients and a condition that might influence pharmacokinetics.

Pharmacokinetic Assessment

Children came to the clinic without having taken breakfast. Darunavir/ritonavir was administered with breakfast. At steady state, blood samples were taken before observed intake and at 2, 3, 4, 6, 8, 12 and 24 hours post-ingestion. The 12-hour sample could be omitted.

Plasma concentrations of darunavir were determined using a validated ultra-high performance liquid chromatography assay with ultraviolet (UV) detection derived from the previously published assay.[7] The analytical range of the assay was 0.10–30 mg/L. The intraday and interday precision ranged from 0.6% to 4.3% (coefficient of variation (CV)) and 0.14% to 2.4%, respectively. The percentage accuracy of the assay ranged from 98.2% to 105.6%. The analysis was performed at the Department of Pharmacy of the Radboudumc that participates in an international interlaboratory quality control program for antiretroviral drugs.[8]

Pharmacokinetic and Statistical Analysis

Darunavir pharmacokinetic parameters were determined using noncompartmental analysis (Phoenix WinNonlin version 6.4, Pharsight Corporation, Cary, North Carolina California). Pharmacokinetic parameters of interest were area under the plasma concentration-time curve over 24 hours (AUC_{0-24}), maximum observed plasma concentration, time of maximum observed plasma concentration, last observed plasma concentration (C_{last}) and clearance (CL/F/kg). Exposure was defined adequate when the lower limit of the 90% one-sided confidence interval (CI) of the geometric mean AUC_{0-24} was above 80% of the value of adults ($0.8 \times 89.7 = 71.8$ h·mg/L).[6] C_{last} should be above the trough plasma concentration target for PI-experienced patients

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(10 × 0.055 = 0.55 mg/L).[9] This often quoted value of 0.55 mg/L has been validated for patients with previous failure on PI-based regimens and is seen as a conservative target for patients without previous PI failure, as were the children in our study.

Sample Size

Darunavir plasma exposure was expected to be similar compared with adults. The geometric mean AUC_{0-24} in adults is 89.7 h·mg/L. A variation coefficient of 29% in AUC_{0-24} was observed in adolescents.[3] Based on a simulation study in SAS (SAS Institute Inc., Cary, North Carolina), inclusion of 12 children provided a power of 80.3% to investigate whether the lower limit of the 90% one-sided CI of the geometric mean of the area under the curve (AUC0-24) is higher than 80% of the value found in adults.

Virologic Assessment and Safety

Children visited the outpatient clinic approximately every 3 months as part of routine clinical care. At these visits, possible adverse effects were discussed and virologic assessment was performed as described previously.[10] In case of detectable viral load, viral load determination was repeated after 1 month. Children were followed-up in the study until inclusion of the last child.

Acceptability Questionnaire

Acceptability of a drug regimen is important for adherence. Aspects such as dosing frequency and ease of administration are important for acceptability. During the day of the pharmacokinetic assessment, children and their parents were asked about the preference for the current or previous antiretroviral regimen.

RESULTS

Population and Treatment

Twelve children were enrolled between July 2015 and August 2016. Demographic data are presented in Table 1. All children used abacavir and lamivudine once-daily as background regimen. The use of other concomitant medication was reported for 2 children (1 child: levetiracetam, valproic acid, clobazam; 1 child: triptorelin). None of these drugs are known to influence darunavir or ritonavir pharmacokinetics.

TABLE 1. Demographic Data of HIV-infected Children and Darunavir Pharmacokinetic Parameters After Once-daily Dosing (n = 12)

Demographic Data	Median (Range)
Sex (female/male)	7/5
Age (yr)	8.9 (6.3–11.7)
Weight (kg)	26.6 (22.4–45.0)
Darunavir dose (mg/kg)	22.6 (17.8–26.8)
Ritonavir dose (mg/kg)	3.8 (2.2–4.5)
Dosing regimen darunavir/ritonavir (n)	
600/100 mg (15–30 kg)	7
675/100 mg (30–40 kg)	2
800/100 mg (from 40 kg)	3
Previous antiretroviral regimen (n)	
Lopinavir/ritonavir twice-daily	9
Lopinavir/ritonavir once-daily	3
Pharmacokinetic parameters, geometric mean (%CV)	
AUC_{0-24} (h·mg/L)	63.1 (33%)
C_{max} (mg/L)	5.6 (34%)
C_{last} (mg/L)	1.5 (44%)
CL (L/h·kg)	0.36 (40%)
T_{max} (h)*	2.6 (2.0–5.9)

*Median (range) value of T_{max} is reported.

C_{max}, indicates maximum observed plasma concentration; CL/F/kg, dose/(AUC0-24 x body weight); CV, coefficient of variation; T_{max}, time of maximum observed plasma concentration; CL, Clearance.

At the day of the pharmacokinetic assessment, the median (range) time on darunavir/ritonavir once-daily was 16 (16–47) days. CL (CL/F/kg) = dose/(AUC_{0-24} × body weight).

Darunavir Pharmacokinetics

The calculated pharmacokinetic parameters of all children (n = 12) were used for the pharmacokinetic model. In 6 children, the 12-hour sample was omitted. The geometric mean (%CV) AUC_{0-24} was 63.1 (33%) h·mg/L, C_{last} was 1.5 (44%) mg/L (Table 1) and the plasma concentration before observed intake (C0) was 1.4 (68%) mg/L. The lower limit of the one-sided 90% CI was 55.7 h·mg/L, which is 62% of the adult value. Therefore, the target of 80% of the adult value was not reached. Ten of the children (83%) had an AUC_{0-24} below the adult mean value, of which 8 (67%) had an AUC below 80% of this value (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/D25).

C_{last} of all of the children was measured between 23.1 and 25.1 hours after the observed intake and all were above 0.55 mg/L (range: 0.69–2.4 mg/L).

Virologic Assessment and Safety

Median (range) duration on the once-daily darunavir/ritonavir regimen was 16 (16–47) days at the day of the pharmacokinetic assessment and median follow-up was 11.6 months (0.5–14.2) at the end of the study. One child had 3 consecutive detectable HIV-RNA measurements (20–200 copies/mL) within a 3-month period but became undetectable again after 3 months without change of antiretroviral regimen. The darunavir/ritonavir dose used by this child was 27 mg/kg, the measured AUC_{0-24} was 65.3 h·mg/L and C_{last} 0.69 mg/L. All other children had an undetectable viral load during the course of the study.

One child suffered from anxiety starting 4 weeks after switch to darunavir/ritonavir and 2 weeks after the pharmacokinetic assessment, resulting in hallucinations at 6 weeks after start. Darunavir/ritonavir was stopped and the child fully recovered within 4 days after discontinuation. This child used 600 mg (24 mg/kg) darunavir and the measured AUC_{0-24} was 47.8 h·mg/L. All other children remained on darunavir/ritonavir once-daily during the course of the study.

Acceptability

All children completed the questionnaire together with their parents. They used lopinavir/ritonavir tablets once-daily (n = 3) or twice-daily (n = 9) before the switch to darunavir/ritonavir once-daily. Ten of the children and 10 of the parents (83%) considered the once-daily darunavir/ritonavir regimen (much) easier compared with the previous regimen. One child had difficulties taking darunavir/ritonavir because of the taste. A once-daily regimen compared with a twice-daily regimen was preferred by most of the children (n = 11). The main reason for the preference was the lower impact on daily activities.

DISCUSSION

This is the first study reporting on the pharmacokinetics, safety and efficacy of the approved once-daily dosing regimen of darunavir/ritonavir in children 6–12 years of age. Exposure (AUC) to darunavir was substantially lower than in adults, when using the recommended once-daily dosing regimen. The approved dosing regimen for this age group was derived from a population pharmacokinetic model predicting a mean AUC in children between 80% and 130% of the adult value of 89.7 h·mg/L.[6] The geometric mean exposure in our pediatric population was 70% of the adult value. Only 4 of the 12 children had an exposure between the predicted

limits, all other had lower exposure. The observed exposure in adolescents and young adults treated with once-daily darunavir/ritonavir was also lower than observed in adults: for example, in the Darunavir Once-daily in treatment-Naive adolescents (DIONE) trial, a geometric mean AUC of 90% of the adult value was found.[3,11,12] In treatment-experienced children 3–6 years of age, using the liquid formulation once-daily, the mean darunavir AUC_{0-24} was 128% of the adult AUC_{0-24}. These children used a higher body-weight-based dose.[4]

The short-term virologic response (median follow-up: 11.6 months) to darunavir/ritonavir once-daily was good in 10 of the 11 (91%) children that remained on darunavir/ritonavir. One child discontinued treatment because of adverse events, which could not be related to a higher exposure. One child had virologic rebound but became undetectable again within 3 months without change of regimen.

It can be debated whether AUC is the best parameter to predict darunavir efficacy, as for most PIs efficacy is correlated with the trough level.[2] For darunavir, no correlation has been found between the observed trough levels (nor AUC) and efficacy, but in clinical studies, trough levels remained widely above the median effective concentration for wild-type HIV-1.[9] C_{last} of the children in our study was at least 10 times higher than this concentration (>0.55 mg/L). Therefore, exposure was in our opinion considered adequate.

The bioavailability of darunavir increases significantly when combined with ritonavir.[9] This indicates an important effect from ritonavir on darunavir absorption and/or first pass metabolism. In the population pharmacokinetic model, exposure to ritonavir was not included as covariate. Moreover, children have a lower gastrointestinal volume than adults, which might influence the amount of darunavir that is dissolved and available for absorption. Especially for a low-solubility class drug such as darunavir, this might be an additional explanation for the observed lower exposure.[13]

In conclusion, we found that the AUC of darunavir in children 6–12 years of age was substantially lower compared with the mean adult value, and as predicted by the population pharmacokinetic model. However, trough levels were all above the target value, which, together with the good short-term virologic outcome, supports the use of the approved darunavir/ritonavir once-daily dosing recommendation in HIV-infected children 6–12 years of age.

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