Pharmacokinetics of two generic co-formulations of lopinavir/ritonavir for HIV-infected children: a pilot study of paediatric Lopimune versus the branded product in healthy adult volunteers

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Objectives: To determine the pharmacokinetic profiles of lopinavir and ritonavir in two newly developed generic co-formulations for HIV-infected children (Lopimune paediatric tablets and granules, 100/25 mg of lopinavir/ritonavir, Cipla Pharmaceuticals), and to compare these with the branded product (Kaletra).

Methods: This Phase I, comparative, open-label, three-period, single-dose, crossover study was designed as a pilot study to exclude large (>40%) differences in the exposure to lopinavir. Single doses of medication, normalized to 400 mg of lopinavir, were administered on an empty stomach, 1 week apart. A 32 h pharmacokinetic curve was recorded. In an additional part of the study, in five of the same volunteers, a pharmacokinetic curve was recorded after administration of the Lopimune granules and Kaletra oral solution, both with food.

Results: Twelve healthy subjects were enrolled (four females). The median (range) age, height and body weight were 24 (21–55) years, 1.79 (1.63–1.95) m and 72 (51–87) kg, respectively. The median [interquartile range (IQR)] AUC0–t of lopinavir was 71.8 (48.8–93.5), 38.7 (28.7–52.2) and 58.7 (42.5–79.4) mg .h/L with Kaletra tablets, Lopimune granules and Lopimune paediatric tablets, all taken on an empty stomach, respectively. The respective Cmax values were 7.2 (5.8–8.3), 4.6 (4.1–5.2) and 6.5 (5.0–7.1) mg/L after intake of the different formulations. When comparing the Lopimune formulations with the reference product Kaletra, for all parameters the differences were statistically significant (P ≤ 0.015). Ritonavir exposure was also lower after intake of the generic formulations versus Kaletra. When the five subjects took the Lopimune granules or Kaletra solution with food, the median (IQR) AUC0–t of lopinavir was 58.5 (55.4–77.6) and 49.6 (39.1–58.1) mg.h/L, respectively.

Conclusions: Large differences in pharmacokinetic parameters can be excluded for Lopimune paediatric tablets when compared with the branded product and taken on an empty stomach, and also for Lopimune granules when these are taken with food.

Keywords: lopinavir, ritonavir, pharmacokinetics, generics

Introduction

HIV mortality in children has decreased 70% since the introduction of protease inhibitor (PI)-containing combinations.1–2 Lopinavir/ritonavir is one of the preferred PIs for adults and children, according to international guidelines.3–5

There are two formulations of lopinavir/ritonavir available for children: (i) an oral solution of 80/20 mg/mL lopinavir/ritonavir (Kaletra™), which has to be stored in a refrigerator and has to be taken with food; and (ii) recently introduced paediatric tablets containing 100/25 mg of lopinavir/ritonavir (Kaletra™), which can be taken with or without food and may be stored at room temperature.

More than 90% of HIV-infected people live in developing countries and, despite increased access, still only a minority of patients that need antiretroviral treatment (ART) receive this therapy.3 A major reason for this is the cost of branded ART. Since 2001, it has been possible for local manufacturers to produce generic antiretroviral drugs, even for medication that is still patented. This has led to a strong reduction in the price of ART in resource-limited parts of the world. As a consequence, there has been an increase in the number of HIV-infected...
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patients receiving therapy. Although this sounds promising, there are still some challenges in treating HIV-infected children in developing countries: not all the antiretroviral drugs are approved to be used in children; there is a lack of pharmacokinetic data on appropriate dosing; branded products are expensive; and oral solutions or suspensions can be difficult to use because of the water that is needed to prepare them, the storage conditions required and their taste.

Since 2008, two generic fixed-dose combinations for HIV-infected children (Triomune Baby and Triomune Junior, produced by Cipla Pharmaceuticals) have been available. These tablets, containing stavudine, lamivudine and nevirapine, are FDA-approved and used as first-line therapy in developing countries.6,7 Cipla has developed two new generic co-formulations for HIV-infected children (Lopimune paediatric tablets and Lopimune granules) containing 100 mg of lopinavir and 25 mg of ritonavir.

The primary objective of this pilot study was to determine the pharmacokinetic profile of lopinavir and ritonavir in Lopimune paediatric tablets and Lopimune granules after a single dose in healthy volunteers and to compare this with the branded product (Kaletra) tablets. This study was conducted as a prelude to a pharmacokinetic study with Lopimune in HIV-infected children in Africa.

Patients and methods

In this Phase I, comparative, single-centre, open-label, three-period, single-dose, crossover pilot study, 12 healthy subjects aged 18–55 years were included. Exclusion criteria were a positive test for HIV, hepatitis B or C, abnormal clinical laboratory test results or the use of concomitant drugs, except for paracetamol. The study protocol was approved by the Ethics Committee of the Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands. Informed consent was obtained from all subjects before enrolment.

Subjects were randomized to one of the following regimen sequences: ABC; ACB; CBA; BAC; CAB; or CBA. The regimens were: Regimen A (reference), two tablets of 20/50 mg of lopinavir/ritonavir (Kaletra tablets, Abbott Laboratories Ltd); Regimen B, four sachets with granules of 100/25 mg of lopinavir/ritonavir (Lopimune granules, Cipla Ltd); and Regimen C, four tablets of 100/25 mg of lopinavir/ritonavir (Lopimune tablets, Cipla Ltd).

Three single doses of medication were administered 1 week apart. Medication was taken orally after ≥2 h of fasting. Meals were standardized and were taken at 2 and 5 h after medication intake.

Blood was collected just before and at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 24 and 32 h after medication intake. Plasma concentrations of lopinavir and ritonavir were determined by a validated HPLC assay with UV detection.8

The pharmacokinetic parameters AUC0–24, Cmax, Tmax and t1/2el were calculated by using non-compartmental pharmacokinetic analysis in the WinNonlin software package (version 5.0 Pharsight Corporation, CA, USA).

Wilcoxon’s signed rank test was used to compare the pharmacokinetic parameters. Descriptive statistics were carried out by using SPSS® software (version 16.0, SPSS Inc.).

After the initial results became known, it was decided to record two additional pharmacokinetic curves in five of the same volunteers after the administration of Regimen D [four sachets with granules of 100/25 mg of lopinavir/ritonavir (Lopimune granules, Cipla Ltd) with food] and Regimen E [5 mL of oral solution containing 80/20 mg/mL lopinavir/ritonavir (Kaletra oral solution, Abbott Laboratories Ltd) with food]. This number was based on the amount of the study medication of the same batch that was left and the availability of the participants.

Results

Twelve healthy Caucasian subjects (four females) were included. The median age, height and body weight (range) were 24 (21–55) years, 1.79 (1.63–1.95) m and 72 (51–87) kg, respectively. All subjects completed the study. Five subjects (two females) also participated in the follow-up study; one subject dropped out after one period (personal reasons).

Plasma concentrations of lopinavir after single doses of the branded product (A), Lopimune granules (B) and Lopimune tablets (C) on an empty stomach are illustrated in Figure 1. Pharmacokinetic parameters of lopinavir and ritonavir after single doses of the different regimens and the results of the Wilcoxon’s signed rank test are shown in Table 1.

Non-parametric statistical tests revealed statistically significant differences in the AUC0–24 and Cmax of lopinavir

Figure 1. Median lopinavir plasma concentrations (mg/L) in 12 healthy volunteers after intake of a single dose of Kaletra tablets (A), Lopimune granules (B) and Lopimune tablets (C) without food.
Table 1. Pharmacokinetic (PK) parameters of lopinavir and ritonavir after the intake of a single dose of Kaletra tablets without food (A) \((n = 12)\), Lopimune granules without food (B) \((n = 12)\) and Lopimune tablets without food (C) \((n = 12)\), and Kaletra tablets without food (A) \((n = 5)\), Lopimune granules with food (D) \((n = 5)\) and Kaletra oral solution with food (E) \((n = 4)\)

<table>
<thead>
<tr>
<th>PK parameters</th>
<th>Kaletra tablets without food (A) ((n = 12))</th>
<th>Lopimune granules without food (B) ((n = 12))</th>
<th>Lopimune tablets without food (C) ((n = 12))</th>
<th>B versus A ((P\ value))</th>
<th>C versus A ((P\ value))</th>
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<tr>
<td>Lopinavir</td>
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<tr>
<td>(AUC_{0-\infty}) (mg·h/L)</td>
<td>71.8 (48.8–93.5)</td>
<td>38.7 (28.7–52.2)</td>
<td>58.7 (42.5–79.4)</td>
<td>0.003</td>
<td>0.015</td>
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<tr>
<td>(C_{\text{max}}) (mg/L)</td>
<td>7.2 (5.8–8.3)</td>
<td>4.6 (4.1–5.2)</td>
<td>6.5 (5.0–7.1)</td>
<td>0.003</td>
<td>0.012</td>
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<tr>
<td>(T_{\text{max}}) (h)</td>
<td>3.0 (3.0–3.8)</td>
<td>3.0 (3.0–3.8)</td>
<td>3.0 (3.0–3.8)</td>
<td>0.673</td>
<td>0.752</td>
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<tr>
<td>(t_{1/2\alpha\beta}) (h)</td>
<td>4.0 (2.9–5.1)</td>
<td>3.9 (3.1–5.2)</td>
<td>3.7 (3.3–4.6)</td>
<td>0.937</td>
<td>0.638</td>
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<tr>
<td>Ritonavir</td>
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<tr>
<td>(AUC_{0-\infty}) (mg·h/L)</td>
<td>3.0 (1.6–4.7)</td>
<td>1.3 (0.8–2.6)</td>
<td>2.3 (1.3–3.0)</td>
<td>0.004</td>
<td>0.019</td>
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<tr>
<td>(C_{\text{max}}) (mg/L)</td>
<td>0.4 (0.4–0.6)</td>
<td>0.2 (0.2–0.4)</td>
<td>0.4 (0.2–0.5)</td>
<td>0.008</td>
<td>0.108</td>
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<tr>
<td>(T_{\text{max}}) (h)</td>
<td>3.0 (2.0–3.0)</td>
<td>3.0 (2.0–3.0)</td>
<td>3.0 (2.0–3.8)</td>
<td>0.625</td>
<td>0.233</td>
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<tr>
<td>(t_{1/2\alpha\beta}) (h)</td>
<td>5.1 (4.2–6.2)</td>
<td>5.1 (4.0–6.2)</td>
<td>4.9 (4.0–6.3)</td>
<td>0.814</td>
<td>0.638</td>
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<td>Lopinavir</td>
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<tr>
<td>(AUC_{0-\infty}) (mg·h/L)</td>
<td>62.1 (43.8–126.3)</td>
<td>58.5 (55.4–77.6)</td>
<td>49.6 (39.1–58.1)</td>
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<tr>
<td>(C_{\text{max}}) (mg/L)</td>
<td>7.2 (4.6–9.1)</td>
<td>6.4 (5.5–7.6)</td>
<td>5.2 (4.3–5.7)</td>
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<tr>
<td>(T_{\text{max}}) (h)</td>
<td>4.0 (3.0–5.0)</td>
<td>6.0 (4.0–6.0)</td>
<td>6.0 (3.8–6.0)</td>
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<td>(t_{1/2\alpha\beta}) (h)</td>
<td>4.2 (3.0–7.0)</td>
<td>4.0 (3.5–4.8)</td>
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<td>Ritonavir</td>
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<tr>
<td>(AUC_{0-\infty}) (mg·h/L)</td>
<td>2.8 (1.2–4.4)</td>
<td>2.0 (1.3–2.5)</td>
<td>1.7 (1.1–2.0)</td>
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<tr>
<td>(C_{\text{max}}) (mg/L)</td>
<td>0.4 (0.2–0.6)</td>
<td>0.4 (0.3–0.6)</td>
<td>0.3 (0.2–0.4)</td>
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<td>6.0 (4.0–6.0)</td>
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<tr>
<td>(t_{1/2\alpha\beta}) (h)</td>
<td>6.2 (4.7–9.0)</td>
<td>3.2 (2.4–4.0)</td>
<td>4.7 (2.6–6.8)</td>
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Values are medians (interquartile range).
between the two Lopimune formulations and the branded product when taken on an empty stomach. No other statistically significant differences were found.

Exposure to lopinavir seemed to be evidently higher when Lopimune granules were taken with food and was comparable when Kaletra tablets were taken without food. Ritonavir showed the same results as lopinavir (Table 1).

No serious adverse events were reported. Adverse events that were possibly or probably related to treatment were diarrhoea (2/12 on Kaletra tablets, 4/12 on Lopimune granules and 5/12 on Lopimune tablets), headache (1/12 on Kaletra tablets and 1/12 on Lopimune granules), increased alanine aminotransferase (grade 1, 1/12 on Kaletra tablets) and restless bowel (1/12 on Lopimune granules). All adverse events occurred after intake on an empty stomach and resolved spontaneously.

Discussion

This pilot study shows that the pharmacokinetic profiles of lopinavir and ritonavir in Lopimune granules and Lopimune paediatric tablets differ from the branded product after the intake of single doses on an empty stomach. Non-parametric statistical tests revealed statistically significant differences in lopinavir AUC0–t and Cmax and ritonavir AUC0–t.

Even though this pilot study was not powered to prove bioequivalence, with 12 subjects it was possible to exclude large differences (>40%) in pharmacokinetic parameters. Based on the results of the first part of this pilot study, these large differences can be excluded for the generic Lopimune paediatric tablets, but not for the generic Lopimune granules.

To rule out that the differences in exposure to lopinavir and ritonavir were caused by a different content of these substances in the various formulations, the content of lopinavir and ritonavir was determined in the three products. No deviations from the declared content were found (data not shown). Because no significant differences were found in Tmax and t1/2, it seemed that the amount absorbed, but not the rate of absorption, was different after the intake of both Lopimune formulations. One of the possible explanations is that the absorption of (especially) the generic granules is dependent on food. For instance, the absorption of lopinavir from Kaletra oral solution was 80% higher when taken with food.9 To investigate this possible explanation, the study was extended in five participants from the original study. In this way, it was possible to perform an intra-subject comparison of the intake of granules with and without food. This number was chosen because study medication of the same batch was available for five subjects and should be sufficient to observe an 80% difference in absorption after intake with versus without food. The same procedures were applied, except that the medication was taken with a standardized breakfast and that Kaletra oral solution was included as a reference product. The absorption of lopinavir and ritonavir was higher from the Lopimune granules taken with food compared with the Kaletra oral solution. Also, in the five subjects in the sub-study, the AUAC0–t of lopinavir was on average 33% higher when the granules were taken with food versus without food. The pharmacokinetic profiles of lopinavir and ritonavir in Lopimune granules taken with food appear to be comparable to the Kaletra tablets taken without food.

Based on our pilot observations, we recommend that both Lopimune formulations should be taken with food in the formal bioequivalence study. Prior to results being available from this study, we believe that the information from this independent pilot study is sufficient to start a larger pharmacokinetic study in African HIV-infected children, who are a key target population for the use of Lopimune. The children in this trial will be closely monitored for potential toxicity and virological failure, because bioequivalence of the Lopimune paediatric tablets and granules still needs to be proven.

In conclusion, large differences in pharmacokinetic parameters can be excluded for the Lopimune tablets when compared with the branded product and taken on an empty stomach, and also for the Lopimune granules when these are taken with food. Based on the results of this pilot study, it is acceptable to start testing the pharmacokinetics and dosing requirements of Lopimune paediatric tablets and granules in HIV-infected children, while monitoring closely for potential toxicity and virological failure.

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Transparency declarations

None to declare.

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6 L’homme RF, Dijkema T, Warris A et al. Pharmacokinetics of two generic fixed-dose combinations for HIV-infected children (Pedimune Baby &

