Pharmacokinetics and pharmacodynamics of indinavir with or without low-dose ritonavir in HIV-infected Thai patients

David Burger1*, Mark Boyd2,3, Chris Duncombe2,3, Mariet Felderhof4, Apicha Mahanontharit2, Kiat Ruxrungtham2, Sasiwimol Ubolyam2, Michael Stek3, David Cooper3, Joep Lange4, Praphan Phanupak2 and Peter Reiss4

1Department of Clinical Pharmacy, 533 University Medical Centre Nijmegen, Geert Grooteplein 8, 6525 GA Nijmegen; 4Academical Medical Centre/International AIDS Therapy Evaluation Centre, Amsterdam, The Netherlands; 2HIV-NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand; 3National Centre in HIV Epidemiology and Clinical Research, Sydney, Australia; 5Merck & Co., Whitehouse Station, NJ, USA

Received 13 January 2003; returned 27 January 2003; revised 7 February 2003; accepted 9 February 2003

Objectives: To describe the pharmacokinetics and pharmacodynamics of indinavir with or without low-dose ritonavir in human immunodeficiency virus (HIV)-infected Thai patients.

Patients and methods: Thirty-six HIV-1-infected patients who participated in HIV-NAT 005 study gave informed consent to record a pharmacokinetic curve 4 weeks after starting a regimen containing either indinavir 800 mg every 8 h (n = 19) or indinavir 800 mg + ritonavir 100 mg every 12 h (n = 17). Indinavir plasma concentrations were measured by HPLC. Pharmacokinetic parameters were calculated by non-compartmental methods.

Results: The median (interquartile range; IQR) body weight of the 36 patients (11 females and 25 males) was 60 (54–72) kg. Median and IQR values for indinavir AUC, Cmax and Cmin were 20.9 (13.1–27.0) mg⋅h/L, 8.1 (6.6–9.4) mg/L and 0.13 (0.09–0.27) mg/L, respectively, for indinavir 800 mg every 8 h, and 49.2 (42.5–60.4) mg⋅h/L, 10.6 (8.5–13.2) mg/L and 0.68 (0.43–0.77) mg/L, respectively, for indinavir 800 mg + ritonavir 100 mg every 12 h. These values are not largely different from values found in Caucasian patients, with the exception of relatively high peak levels of indinavir in Thai subjects. Cut-off values for optimal virological efficacy were an indinavir Cmin of 0.10 and 0.25 mg/L for the every 8 h and the every 12 h regimen, respectively; patients with an indinavir AUC greater than 30 (every 8 h regimen) or 60 (every 12 h regimen) mg⋅h/L were at increased risk of developing nephrotoxicity.

Conclusions: Indinavir pharmacokinetics and pharmacodynamics in Thai HIV-1-infected patients are similar to those described in Caucasian patients, despite an overall lower body weight in this population.

Keywords: HIV, protease inhibitors, Thailand

Introduction

Indinavir is a human immunodeficiency virus (HIV) protease inhibitor with a documented efficacy lasting more than 5 years.1 From a pharmacokinetic perspective, its major disadvantages are limited absorption when taken with food, a short elimination half-life that necessitates frequent (i.e. every 8 h) dosing, and adverse effects that have been related to increased exposure to indinavir.2–5 Some of these disadvantages are ameliorated by combining indinavir with ritonavir. Ritonavir inhibits hepatic metabolism of indinavir and as a result its elimination half-life is prolonged.6–9 Furthermore, the combination of indinavir plus

*Corresponding author. Tel: +31-24-3616405; Fax: +31-24-3540331; E-mail: D.Burger@akf.umcn.nl

© 2003 The British Society for Antimicrobial Chemotherapy
ritonavir can be taken in an every 12 h regimen and with food. Because of this convenience, most patients on indinavir are now taking the drug together with ritonavir.

Because of the expected advantages of boosting indinavir plasma levels with ritonavir, a clinical trial comparing the original 800 mg every 8 h dose of indinavir with the new regimen containing indinavir 800 mg + ritonavir 100 mg every 12 h, both taken with zidovudine plus lamivudine, was initiated at the HIV-NAT clinical trials centre in Bangkok, Thailand. As no data were available on the pharmacokinetics of indinavir (with or without ritonavir) in Thai patients, a pharmacokinetic substudy was conducted. Because Thai patients are known to have significantly lower body weights than Caucasian patients, there was concern for increased exposure to indinavir, potentially resulting in increased toxicity in these Thai subjects. A secondary objective was to evaluate whether relationships between the pharmacokinetics of indinavir and its pharmacodynamics could be observed, similar to what had been reported in Caucasians (for review, see Acosta et al.11).

Materials and methods

Patients

Patients in HIV-NAT 00510 were randomized to receive indinavir 800 mg every 8 h or indinavir 800 mg + ritonavir 100 mg every 12 h; all patients additionally received zidovudine 300 mg plus lamivudine 150 mg (Combivir) every 12 h. Patients had received at least 3 months of treatment with zidovudine, either alone or in combination with didanosine (ddI) or zalcitabine (ddC) before inclusion in the 005 study. For this pharmacokinetic substudy, subjects were randomly selected from the cohort of HIV-NAT 005 participants. The Ethics Committee of the Faculty of Medicine, Chulalongkorn University, approved the study, and written informed consent was obtained from all patients before enrolment.

Pharmacokinetic analysis

Four weeks after start of treatment, patients were admitted to the HIV-NAT outpatient clinic to determine the steady-state pharmacokinetics of indinavir. Patients took an 800 mg dose of indinavir on an empty stomach (every 8 h regimen, without ritonavir) or together with a light meal (every 12 h regimen, with ritonavir; 10–15 g fat; 400–700 kcal). Blood samples were collected just before and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7 and 8 h post-ingestion. For the every 12 h regimen, blood was also sampled at t = 10 and 12 h post-ingestion. Plasma was separated by centrifugation and samples were stored at –20°C until analysis. Indinavir and ritonavir concentrations were determined in plasma by HPLC, as previously reported.12 Pharmacokinetic parameters were calculated in Microsoft Excel 97 by non-compartmental methods.13 The highest observed plasma concentration was defined as $C_{\text{max}}$, with the corresponding sampling time as $T_{\text{max}}$. The terminal, log-linear period ($\log C$ versus $T$) was defined by the last data points ($n > 2$) by visual inspection. The absolute value of the slope ($\beta/\ln(10)$) was calculated by least-squares analysis. The elimination half-life ($t_{1/2}$) was calculated using the equation $t_{1/2} = \ln(2)/\beta$.

The area under the curve (AUC) was calculated using the trapezoidal rule for $t_0$ to $t_8$ (every 8 h regimen) or $t_{12}$ (every 12 h regimen).

Pharmacokinetic/pharmacodynamic relationships

The relationship between the plasma concentrations of indinavir and its antiviral activity effect was investigated during the first 6 months of treatment. Antiviral response was defined as having a viral load <50 copies/mL, as measured by Chiron bDNA v3, at 6 months. The relationship between indinavir pharmacokinetics and toxicity was investigated by a detailed analysis of indinavir-induced adverse effects on renal function. Indinavir-induced nephrotoxicity based on information actively collected at 4 week intervals during the first 12 weeks of treatment was defined as having either flank pain, haematuria, or an increase in serum creatinine of >25% from baseline.

Statistics

Correlations between indinavir pharmacokinetic parameters and body weight or body surface area were analysed by least squares regression analysis. Receiver Operating Characteristic (ROC) curves were drawn to detect breakpoints of pharmacokinetic parameters that were possibly related to a pharmacodynamic effect. Subsequently, the study population was divided in two groups of patients who had either a parameter value below or above this breakpoint. Mann–Whitney U-test and Pearson’s $\chi^2$ test were used for comparison of pharmacokinetic parameters between subgroups. All statistical tests were carried out using SPSS for Windows version 9.0 (SPSS Inc., Chicago, IL, USA).

Results

Nineteen patients were included in the 800 mg every 8 h arm and 17 patients in the indinavir 800 mg plus ritonavir 100 mg every 12 h arm. Patient demographics are listed in Table 1. Indinavir plasma concentration versus time curves for both regimens are presented in Figure 1. Median + interquartile range (IQR) values of the relevant pharmacokinetic parameters are listed in Table 2. For comparison, data from the literature on Caucasian patients6,8 are given in the same table. No major differences between Thai and Caucasian patients were observed, with the exception of an ~20% higher $C_{\text{max}}$ of indinavir and an ~35% shorter $t_{1/2}$ in both regimens in the Thai...
Pharmacokinetics and pharmacodynamics of indinavir

Table 1. Demographics of the patients

<table>
<thead>
<tr>
<th></th>
<th>Indinavir 800 mg every 8 h</th>
<th>Indinavir 800 mg + ritonavir 100 mg every 12 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>13/6</td>
<td>12/5</td>
</tr>
<tr>
<td>Age (years)</td>
<td>34 (30–36)</td>
<td>36 (32–41)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>60.5 (52.7–67.5)</td>
<td>59.2 (54.2–73.6)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.68 (1.62–1.73)</td>
<td>1.63 (1.55–1.79)</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.69 (1.53–1.78)</td>
<td>1.63 (1.55–1.79)</td>
</tr>
<tr>
<td>CD4 cell count (mm⁻³)</td>
<td>84 (16–315)</td>
<td>207 (69–265)</td>
</tr>
<tr>
<td>Viral load (log₁₀ copies/mL)</td>
<td>4.1 (3.4–4.5)</td>
<td>4.0 (3.6–4.3)</td>
</tr>
</tbody>
</table>

Data are medians with interquartile ranges in parentheses.

Figure 1. Indinavir plasma concentration versus time curves of both regimens. Data are median values.

patients. Ritonavir pharmacokinetic parameters are also listed in Table 2; no major differences with values reported in Caucasian patients were observed.

The median (IQR) body weight of the 36 patients was 60 (54–72) kg. To evaluate possible relationships between body weight and indinavir exposure, individual values of indinavir AUC and \( C_{\text{max}} \) are plotted against body weight (Figure 2). In all analyses, lower body weights were associated with higher indinavir exposure, but this only reached statistical significance for the indinavir \( C_{\text{max}} \) in the every 8 h regimen (\( r = 0.52; P = 0.02 \)). Body weight and \( C_{\text{min}} \) values were not related (data not shown). Substituting body surface area for body weight in these calculations demonstrated similar correlations (data not shown).

Six subjects in the every 8 h regimen (32%) and five subjects in the every 12 h regimen with low-dose ritonavir (29%) were females. There was a trend towards higher exposure of indinavir in female patients, especially with regard to AUC and \( C_{\text{max}} \), but this did not reach statistical significance in any of the comparisons.

Three of the 19 patients in the every 8 h group and four of the 17 patients in the every 12 h group had a virological failure (defined as a viral load >50 copies/mL after 24 weeks of treatment). Relationships between indinavir \( C_{\text{min}} \) values and
virological failure were observed (Table 3). For the every 8 h regimen, this reached statistical significance with a $C_{\text{min}}$ of 0.10 mg/L as the cut-off value; for the every 12 h regimen with low-dose ritonavir, the cut-off value was 0.25 mg/L. A similar trend was also observed for AUC (cut-off values 14 and 42 mg h/L for the every 8 h and every 12 h regimen, respectively) but this did not reach statistical significance ($P = 0.15$ for both groups).

Six patients in the every 8 h regimen and four patients in the every 12 h regimen fulfilled the criteria for indinavir-related nephrotoxicity (defined as either flank pain, haematuria or an increase in serum creatinine of >25% within the first 12 weeks of treatment). Again, relationships with drug exposure could be observed, particularly with respect to the AUC that was achieved: cut-off values were 30 and 60 mg h/L for the every 8 h and the every 12 h regimens, respectively ($P = 0.036$ and $P = 0.022$). $C_{\text{max}}$ was also significantly associated with a higher likelihood of nephrotoxicity in the every 12 h regimen, but not in the every 8 h regimen.

Because in clinical practice, it is unknown when $C_{\text{max}}$ is achieved in an individual patient, we have searched for a fixed time point that could be used to detect a toxic indinavir plasma level. It appeared that the indinavir plasma level at 2 h post-ingestion was highly predictive for the development of nephrotoxicity in both indinavir regimens. For patients using indinavir 800 mg every 8 h in this study, only two of the 12 subjects with a 2 h indinavir level <7.5 mg/L had signs of nephrotoxicity versus four out of seven subjects with a 2 h level above this value ($P = 0.07$). For the patients using indinavir 800 mg + ritonavir 100 mg every 12 h in this study, only one of the 11 subjects who had a 2 h indinavir level <10.0 mg/L had signs of nephrotoxicity versus three out of six of the patients with a 2 h indinavir level above this threshold ($P = 0.01$).

### Discussion

HIV-NAT 005 is the first randomized controlled clinical trial comparing indinavir 800 mg every 8 h with indinavir 800 mg plus ritonavir 100 mg every 12 h in indinavir-naive patients. Following 76 weeks of treatment, it was concluded that the every 12 h regimen with low-dose ritonavir was as effective as the every 8 h regimen without ritonavir, though a trend was observed towards more adverse events, drug interruptions and hyperlipidaemia in the every 12 h regimen. Approximately two-thirds of the patients in both arms had an undetectable viral load (<50 copies/mL) by intention-to-treat analysis, which resembles data observed in clinical studies in Europe and North America.

The pharmacokinetic data as presented in this paper do not indicate an effect of Asian race on indinavir pharmacokinetics. Despite a relatively low body weight in this Thai
Pharmacokinetics and pharmacodynamics of indinavir

study population (median value 60 kg), median values of pharmacokinetic parameters of indinavir were not distinct from those usually observed in Caucasian subjects. There was a weak trend for patients with low body weight to have more elevated indinavir plasma levels, indicating that very low body weight (e.g. <55 kg) may put patients particularly at risk for elevated exposure to indinavir, in particular $C_{\text{max}}$ (Figure 2b).

Figure 2. (a) Correlation between body weight and indinavir AUC in both regimens; (b) correlation between body weight and indinavir $C_{\text{max}}$ in both regimens.
It has been suggested before that female patients are at a higher risk for toxic plasma concentrations of indinavir than male patients. A similar trend was observed here. Given the fact that women usually have lower body weights, it is difficult to distinguish between these two factors. This study was too small to carry out multivariate analyses.

Several relationships between indinavir exposure and antiviral response or nephrotoxicity could be observed (Table 3), though not all reached statistical significance. This may be the result of the relatively small number of patients included in this study. Furthermore, adherence was not assessed and this may have confounded potential pharmacokinetic–pharmacodynamic relationships. The fact that even with these limitations significant relationships were observed for some pharmacokinetic parameters (e.g. $C_{\text{min}}$ with virological failure, and AUC and $C_{\text{max}}$ with nephrotoxicity) must be explained by the quality of the pharmacokinetic data (i.e. full pharmacokinetic curves) and the strong intrinsic relationship between indinavir pharmacokinetics and its pharmacodynamics. The threshold as found in this study for the indinavir $C_{\text{min}}$ in the 800 mg every 8 h regimen resembles the values observed in other studies of indinavir-naive Caucasian patients using the same indinavir dose. The threshold of 0.25 mg/L that we observed in the indinavir 800 mg plus ritonavir 100 mg every 12 h regimen indicates that a relationship between drug exposure and virological failure also exists for an indinavir regimen that is boosted with a low dose of ritonavir. Intuitively, indinavir $C_{\text{min}}$ thresholds would be expected to be similar in both regimens. Had this been the case, not a single patient in the every 12 h regimen would have been predicted to fail given that all patients in this regimen had indinavir trough levels above 0.10 mg/L. Also, when AUC values for both indinavir regimens were transformed to a 24 h scale in order to make a meaningful comparison of both data sets, the AUC$_{0-24}$ cut-off value for predicting virological failure was not similar for both regimens: 42 and 84 mg/L per h for the every 8 h and the every 12 h regimen, respectively. The reasons for this are as yet unknown, but it should be considered as a warning against extrapolation of pharmacokinetic–pharmacodynamic relationships for the same drug from one dose regimen to another.

Significant relationships between the early development of nephrotoxicity and AUC and $C_{\text{max}}$ (the latter only for the every 12 h regimen) were observed, which is in line with previous observations for the every 8 h regimen. Because the occurrence of nephrotoxicity is caused by precipitation of indinavir crystals in the renal tubules, it is not unexpected that a positive relationship with AUC and $C_{\text{max}}$ was also found for the ritonavir-boosted regimen. Given the fact that the indinavir AUC is higher for the ritonavir-boosted every 12 h regimen than for the unboosted every 8 h regimen (98.4 versus 62.7 mg h/L for the median normalized 24 h AUCs of both regimens), it may be predicted that more nephrotoxicity will occur in the every 12 h regimen. Such a (non-significant) trend in this direction was indeed observed in the overall study population of HIV-NAT 005: 19% versus 30% of patients developed clinical nephrolithiasis on the every 8 h and every 12 h regimen, respectively.

Although the $C_{\text{max}}$ of indinavir in the every 8 h regimen was not found to be significantly related to the development of nephrotoxicity, the threshold values observed for the every 12 h regimen may be considered as a warning against extrapolation of pharmacokinetic–pharmacodynamic relationships from one dose regimen to another.

### Table 3. Pharmacokinetic–pharmacodynamic relationships between indinavir and virological failure or nephrotoxicity

<table>
<thead>
<tr>
<th></th>
<th>Virological failure</th>
<th>Nephrotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>breakpoint (mg/L)</td>
<td>N</td>
</tr>
<tr>
<td>Indinavir 800 mg every 8 h</td>
<td>AUC (mg h/L)</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>$C_{\text{max}}$ (mg/L)</td>
<td>7.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>$C_{\text{min}}$ (mg/L)</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Indinavir 800 mg + ritonavir 100 mg every 12 h</td>
<td>AUC (mg h/L)</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>$C_{\text{max}}$ (mg/L)</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>$C_{\text{min}}$ (mg/L)</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13</td>
</tr>
</tbody>
</table>

For definitions, see text.
nephrotoxicity, a more detailed post-hoc analysis of indinavir plasma levels at fixed time-points suggests that 7.5 mg/L can be used as a threshold for an indinavir plasma level at 2 h post-ingestion for patients using indinavir 800 mg every 8 h. For the indinavir 800 mg + ritonavir 100 mg every 12 h regimen, this indinavir plasma level at 2 h post-ingestion should be below 10.0 mg/L. This makes the indinavir plasma level at 2 h post-ingestion an attractive tool in the prevention or management of indinavir-induced nephrotoxicity. Nephrotoxicity has been an important reason for discontinuation of indinavir. Our data indicate that therapeutic drug monitoring could be used to detect people at risk for discontinuation of indinavir because of nephrotoxicity. A roll-over protocol with the purpose of evaluating whether down-dosing of indinavir under the guidance of therapeutic drug monitoring is effective in the management of indinavir-induced nephrotoxicity is currently ongoing for patients who participated in the HIV-NAT 005 trial.

The use of therapeutic drug monitoring was part of the Athena study, which indeed showed that therapeutic drug monitoring of indinavir resulted in a lower number of patients who discontinued indinavir due to toxicity. These observations are in line with those from Solas et al. who found that patients on indinavir/ritonavir 800/100 mg every 12 h who had trough indinavir levels above 0.5 mg/L had an increased risk of toxicity. Future studies are needed to determine whether using an algorithm based on trough levels (as done by Solas et al.5) or on 2 h post-ingestion levels (as developed by us) is to be preferred.

In conclusion, it was demonstrated that indinavir pharmacokinetics were roughly similar in Thai patients when compared with data reported in the literature for Caucasian patients, despite a lower body weight in the Thai study group. Correlations between body weight and relevant pharmacokinetic parameters were weak, indicating that only patients with very low body weight (<55 kg) may be at increased risk for toxicity. As was demonstrated in Caucasians, significant relationships between indinavir pharmacokinetics and pharmacodynamics were also observed in this Thai study population, highlighting a role for therapeutic drug monitoring in patients using indinavir with or without ritonavir.

References
