Once- or twice-daily dosing of nevirapine in HIV-infected adults: a population pharmacokinetics approach

José Moltó1,2*, Marta Valle2,3, Cristina Miranda1, Samandhy Cedeño4, José Miranda1, José Ramón Santos1, Eugenia Negredo1, Josep Vilaró5, Joan Costa6 and Bonaventura Clotet2,4

1’Lluita contra la SIDA’ Foundation, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; 2Universidad Autónoma de Barcelona, Barcelona, Spain; 3Centre d’Investigació del Medicament, Institut de Recerca de l’Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; 4’IrsiCaixa’ Foundation, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; 5Department of Internal Medicine, Hospital de Vic, Vic, Spain; 6Department of Clinical Pharmacology, Hospital Universitari Germans Trias i Pujol, Badalona, Spain

Received 1 April 2008; returned 19 May 2008; revised 30 May 2008; accepted 3 June 2008

Objectives: The aim of this study was to develop and validate a population pharmacokinetic model for nevirapine in a population of HIV-infected adults and to evaluate the influence of nevirapine dosing regimen and patient characteristics on nevirapine trough concentration.

Methods: HIV-infected adults receiving oral nevirapine for at least 4 weeks were included. A concentration–time profile was obtained for each patient, and nevirapine concentrations in plasma were determined by HPLC. Pharmacokinetic parameters, inter-individual variability and residual error were estimated using non-linear mixed effects modelling. The influence of patient characteristics on the pharmacokinetics of nevirapine was explored, and the predictive performance of the final model was evaluated in an external data set of observations.

Results: Totals of 40 and 18 Caucasian patients were included in two data sets for model building and model validation, respectively. A mono-compartmental model with first-order absorption and elimination best described the pharmacokinetics of nevirapine. Body weight influenced oral clearance (CL/F) and volume of distribution (V/F). The estimated population pharmacokinetic parameters (inter-individual variability) for an individual weighing 70 kg were CL/F 2.95 L/h (24%), V/F 95.2 L (30%) and k11.2 1.8 h−1 (96%). The final model predicted nevirapine concentrations in the external model-validation data set with no systematic bias and adequate precision. Bayesian estimates of nevirapine trough concentrations were lower when nevirapine was administered once instead of twice daily, and nearly half of the patients weighing 90 kg had drug concentrations <3.0 mg/L when nevirapine was dosed once daily.

Conclusions: A population model to describe the pharmacokinetics of nevirapine was developed and validated in HIV-infected patients. Body weight influenced CL/F and V/F. Based on Bayesian estimates of individual nevirapine concentrations, twice- instead of once-daily administration of nevirapine would be more optimal in patients weighing >70 kg.

Keywords: antiretroviral agents, non-linear mixed effects models, suboptimal concentrations, body weight

Introduction

Nevirapine is a non-nucleoside reverse transcriptase inhibitor whose efficacy and safety in the treatment of HIV-infected patients has been shown in several clinical trials.1–3 The approved dosage of nevirapine in HIV-infected adults is 200 mg twice daily.4 However, based on its long plasma half-life and on previous pharmacokinetic data comparing nevirapine exposure under once- or twice-daily nevirapine therapy,5,6 once-daily dosing of nevirapine (400 mg once daily) is also used in clinical practice.
Population pharmacokinetics of nevirapine

Several studies have examined the relationship between exposure to nevirapine and virological response. In a retrospective analysis of the INCAS trial,7 nevirapine concentrations in plasma were related to the virological response in the short (2 weeks) as well as in the long (52 weeks) term. In addition, de Vries-Sluijs et al.8 showed that the risk of virological failure in patients who were receiving nevirapine-based antiretroviral therapy increased 6-fold when nevirapine plasma concentrations were <3.0 mg/L compared with patients with higher concentrations. As a result, current guidelines for therapeutic drug monitoring of antiretroviral agents recommend 3.0 mg/L as the cut-off value for nevirapine trough concentrations. Nevertheless, this cut-off has been questioned based on results observed in the 2NN study, where no evident relationship between nevirapine concentrations and virological response was found.10 On the other hand, although some authors have proposed a role for drug exposure in driving toxicity,11 such a role has not been confirmed in other studies and no nevirapine concentration cut-off value that can predict drug toxicity has been clearly established to date.12

The pharmacokinetic profile of nevirapine is characterized by high oral bioavailability, moderate binding to plasma proteins and prolonged elimination.4,5 In addition, nevirapine concentrations in plasma seem to vary greatly in HIV-infected individuals in clinical practice.13 Moreover, although daily exposure (AUC24) to nevirapine with the 400 mg once-daily regimen was similar to that observed with the 200 mg twice-daily dosing regimen in the study by van Heeswijk et al.,6 nevirapine trough concentration was significantly lower for the once-daily regimen. As a consequence, a significant proportion of patients may not achieve high enough drug concentrations to effectively suppress viral replication. Moreover, viral mutations conferring high-level resistance to nevirapine and other non-nucleoside reverse transcriptase inhibitors are easily selected when viral replication occurs in the presence of the drug,14–16 which highlights the importance of maintaining optimal nevirapine concentrations throughout the dosing interval.

Knowing individual factors affecting variability in nevirapine pharmacokinetics could be very useful for achieving a desired target drug concentration in each patient. Therefore, the objective of the present study was to develop and validate a population pharmacokinetic model for nevirapine and to identify characteristics that might explain inter-individual variability in the pharmacokinetics of nevirapine in a population of HIV-infected adults routinely attending an outpatient HIV clinic. In addition, the influence on nevirapine trough concentration of the dosing regimen and changes in patient characteristics were assessed.

Methods

Patients included in this cross-sectional study were HIV-infected and aged 18 years or older. They had all been receiving stable antiretroviral therapy with oral nevirapine (Viramune®, Boehringer, Ingelheim GmbH, Ingelheim am Rhein, Germany) in routine clinical practice for at least 4 weeks. Self-reported treatment adherence <90% within the previous 2 weeks, active alcohol consumption (>50 g/day) and concomitant administration of other drugs known to affect nevirapine pharmacokinetics were considered exclusion criteria. The study was approved by the Ethics Committee of the reference hospital (Hospital Universitari Germans Trias i Pujol), and all subjects gave their written consent before enrolment.

Demographic and clinical variables, including age, sex, body weight, height, time since HIV diagnosis, hepatitis C virus (HCV) antibodies, hepatitis B virus surface antigen and concomitant medications including over-the-counter drugs, were recorded for each participating patient. In addition, a complete blood cell count, analysis of serum chemistry (including creatinine, total protein, albumin, total bilirubin, aspartate aminotransferase and alanine aminotransferase), CD4+ T lymphocyte count and HIV-1 RNA load were determined/ performed.

Sample collection and analytical determination

A full concentration–time profile was obtained for each participating patient, and blood samples were collected immediately before (0), and 1, 2, 4, 6, 8, 10 and 12 h after a witnessed morning dose of nevirapine. In addition, 62 samples were drawn between 7 and 24 h after drug intake from eight patients who received nevirapine once daily at night. Patients were asked to record the time they had last taken a nevirapine dose on the day before the visit, and the exact times of the nevirapine dose and blood sampling during the visit were recorded.

Blood samples for the determination of drug plasma concentrations were collected in potassium and ethylenediaminetetraacetic acid-containing 10 mL tubes. Plasma was isolated by centrifugation (4000 rpm for 15 min) and stored at −20°C until analysis. Nevirapine concentrations were determined using 200 μL of plasma by HPLC with a photodiode array detector (2996 Waters, Barcelona, Spain). The analytical column was a NovaPak C18 3.9 × 150 mm with a NovaPak C18 column guard (Waters). The method involved precipitation of proteins with 3% HClO4 (200 μL). The supernatant was injected and the drug was resolved by isocratic elution with phosphate-buffered acetonitrile containing 0.1% triethylamine (pH 6). The method was linear over a concentration range of 0.1–10 mg/L. The inter-day coefficients of variation for nevirapine concentrations of 0.2, 3 and 7 mg/L were 8.7%, 1.8% and 3.1%, respectively. The intra-day coefficients of variation for nevirapine concentrations of 0.2, 3 and 7 mg/L were 2.1%, 0.7% and 1.4%, respectively. The assay was externally controlled by the International Interlaboratory Quality Control Program for Therapeutic Drug Monitoring in HIV Infection (KKGT, Nijmegen, The Netherlands).17

Pharmacokinetic analysis

Non-linear mixed effects modelling was performed with the computer program NONMEM (version V, Globomax LLC, Hanover, MD, USA),18 using a Fortran compiler (Compaq Visual Fortran Version 6.0, Compaq Computer Corporation, Houston, TX, USA). NONMEM uses mixed effects (fixed and random) regression to estimate population means and variances of the pharmacokinetic parameters and to identify factors that may influence them. All models were fitted using the first-order conditional estimation procedure with interaction between inter-individual and residual variability. Relative standard error of the parameter estimates was calculated using the COVARIANCE option in NONMEM. The POST-HOC option was used to obtain individual predictions.

Structural model

Disposition characteristics of nevirapine were determined by fitting mono- and bi-compartmental models, with linear and non-linear elimination, to the data. To describe drug absorption, models assuming either a first- or zero-order rate of absorption with and without absorption lag-time were tested.
Statistical model

Exponential errors following a log-normal distribution were assumed for the description of inter-individual variability in pharmacokinetic parameters, as shown in the following equation:

$$\theta_i = \theta \cdot \exp(\eta_i)$$

where $\theta_i$ is the pharmacokinetic parameter of the $i$th individual, $\theta$ is the typical population value and $\eta_i$ is the inter-individual random effect with a mean 0 and a variance $\sigma^2$.

The validity of the inter-individual variability model was assessed by evaluating correlations between individual random effects ($\eta$) for all the pharmacokinetic parameters. When substantial correlation was present, covariances between these parameters were included in the model.

Residual variability (reflecting the difference between the observed and model-predicted concentrations) was modelled initially with a combined error model. If one of the components (additive or proportional) of the residual error was negligible, it was deleted from the model.

Covariate model

Once a model providing an adequate description of the data without the incorporation of covariates was selected, the influence of patients’ characteristics on the variability of the pharmacokinetic parameters was explored for significance by implementing the generalized additive model (GAM) approach in the software Xpose, version 3.1 (Uppsala University, Uppsala, Sweden). This approach enables straightforward display of the role of the various covariates. It uses a stepwise method, where each covariate is introduced in the model through specified linear or non-linear representations. At each step, the model is improved by the addition of the single term that results in the largest decrease in the Akaike information criterion (AIC). The search stops when AIC reaches a minimum value. The covariates initially selected during the GAM analysis were further tested for significance in NONMEM, using the forward inclusion and backward elimination approach.

Selection between models was based on the precision of the parameter estimates, goodness-of-fit plots and the minimum value of the objective function (OF) provided by NONMEM. A covariate was introduced into the model when its inclusion decreased the OF by at least 3.84 points ($P < 0.05$) and reduced the inter-patient variability in the parameters. During the backward elimination procedure, a covariate was only retained in the model when its influence was statistically significant ($P < 0.01$). An OF with an approximate $\chi^2$ distribution with 1 degree of freedom was the basis for these criteria.

Model validation

The final model was internally validated by means of Monte Carlo simulations. One thousand individual concentration–time profiles were generated for individuals receiving nevirapine 200 mg twice daily or 400 mg once daily using the fixed and random population estimates obtained from the model. The median profile and the intervals includ-

Influence of nevirapine dosing regimen and covariates on nevirapine trough concentrations

Three thousand individual concentration–time profiles were generated for each nevirapine dose (200 mg twice daily or 400 mg once daily); one thousand for individuals with a covariate value corresponding to the median, one thousand for patients on the 10th percentile of the range of the covariable and one thousand for patients on the 90th percentile of the range of the covariable. The median profile of the simulated concentrations for each category was plotted together. Mean predicted nevirapine trough concentrations and the proportion of patients with nevirapine trough concentrations $<3.0$ mg/L were compared between different categories using the $t$-test and the $\chi^2$ test, respectively.

Results

A total of 319 nevirapine observations from 40 Caucasian patients was included in the model-building data set. A median (range) of 8 (8–15) samples per subject were available. Nevirapine dose was 200 mg twice daily in 14 patients, 400 mg once daily in the morning in 18 patients and 400 mg once daily at night in the remaining 8 patients. Table 1 summarizes the characteristics of the patients studied.

Nevirapine concentrations ranged between 2.2 and 10.3 mg/L [coefficient of variation (CV) 36%] in patients receiving 200 mg of nevirapine twice daily, and from 2.5 to 16.1 mg/L (CV 32%) in patients receiving 400 mg of nevirapine once daily (Figure 1). A mono-compartmental model with first-order absorption and elimination best described the population pharmacokinetics of nevirapine. Models with zero-order absorption and two compartments were also studied but did not adequately fit the data. The introduction of an absorption lag-time did not improve the pharmacokinetic model ($\Delta$OF $-3.3$). In addition, although the introduction of inter-individual variability in bioavailability significantly decreased the OF ($\Delta$OF $-7.1$), it increased the relative standard error of the pharmacokinetic estimates and did not improve agreement between observed and predicted data. Finally, as the additive component of the residual error was negligible, and the OF remained unchanged when that component was deleted from the model, only the proportional component of the residual error was retained in the final model. Table 2 lists the fixed and random effects estimated in the model without covariates.

The model-building steps for the covariate analysis are summarized in Table 3. None of the covariates except body weight improved the model when they were included in the pharmacokinetic parameters of nevirapine. Inclusion of body weight in oral clearance (CL/F) resulted in a significant improvement of goodness of fit ($\Delta$OF $-36.7$). Similarly, the introduction of body weight in volume of distribution (V/F) improved the fit in an external data set of observations collected in another study where a subset of patients received nevirapine-based antiretroviral therapy (model-validation data set). The fixed and random estimates obtained from the models were used to predict individual nevirapine concentrations, which were plotted and compared with actual concentration values. Mean prediction error and root mean squared error, and their 95% confidence intervals (CIs), were calculated as a measure of bias and precision, respectively.
(ΔOF = 9.9) and reduced the inter-individual variability of V/F by 13.8%. Finally, when body weight was included in both CL/F and V/F, there was an additional improvement in goodness of fit (ΔOF = 9.7). The parameter estimates for the final model are given in Table 2.

**Model validation**

Figure 1 shows the average population prediction with the 90% prediction interval for each nevirapine dosing regimen, and Figure 2 depicts the overall goodness of fit of the final pharmacokinetic model to the data. The prediction interval obtained with the final model encompassed the observed concentration–time data adequately. The proportion of nevirapine concentrations outside the 90% prediction interval was 9.2% in patients receiving 400 mg of nevirapine once daily, and 11.4% in patients receiving 200 mg of nevirapine once daily. Individual predictions of nevirapine trough concentrations were 3 mg/L in all six patients who had suboptimal trough concentrations.

External validation of the model was performed in a total of 88 observations from 18 patients, which were included in the model-validation data set (Table 1). Individual nevirapine predictions versus actual concentrations in the model-validation data set are shown in Figure 3. The performance of the individual predictions was satisfying, and mean (95% CI) bias and precision were 3.4% (−0.5 to 6.3) and 8.4% (5.9–10.7), respectively.

**Influence of nevirapine dosing regimen and covariates on nevirapine trough concentrations**

In order to elucidate their possible clinical relevance, the influence of nevirapine dosing regimen and patients’ body weight on the population prediction of nevirapine concentrations was further investigated. Figure 4 shows steady-state nevirapine concentration profiles predicted for typical individuals weighing 50, 70 and 90 kg and undergoing antiretroviral therapy with nevirapine at a 200 mg twice-daily or at a 400 mg once-daily dosing regimen.

Overall, the mean (SD) predicted nevirapine trough concentration was 5.35 (1.97) mg/L in patients receiving 200 mg of nevirapine twice daily, compared with 4.33 (1.80) mg/L in patients receiving 400 mg of nevirapine once daily (P < 0.01). In addition, higher body weight was associated with a lower predicted nevirapine concentration. Consequently, the proportion of individuals with predicted nevirapine trough concentrations

| Table 1. Demographic characteristics of the patients included in the model-building and in the model-validation data sets |
|-------------------------------------------------|-----------------|-----------------|
| **Model building n = 40**                       | **Model validation n = 18** |
| Sex (male)                                      | 31 (77.5)       | 12 (67.0)       |
| Age (years)                                     | 50.8 (23.0)     | 40.7 (9.4)      |
| Weight (kg)                                     | 67.9 (12.0)     | 69.1 (12.6)     |
| Height (m)                                      | 1.67 (0.09)     | 1.67 (0.07)     |
| Time since HIV diagnosis (years)                | 9.1 (4.8)       | 8.4 (4.3)       |
| HCV/HBV co-infection†                            | 3 (7.5)         | 4 (22.0)        |
| Time on nevirapine therapy (weeks)              | 141.3 (122.3)   | 213.1 (103.2)   |
| NVP dosing regimen†                              |                |                 |
| 200 mg bid                                      | 14 (35.0)       | 14 (77.8)       |
| 400 mg qd morning                              | 18 (45.0)       | 2 (11.1)        |
| 400 mg qd night                                | 8 (20.0)        | 2 (11.1)        |
| Reverse transcriptase inhibitors†               |                |                 |
| zidovudine                                      | 3 (7.5)         | 0               |
| lamivudine                                      | 31 (77.5)       | 14 (77.8)       |
| stavudine                                       | 1 (2.5)         | 0               |
| didanosine                                      | 15 (37.5)       | 2 (11.1)        |
| abacavir                                       | 9 (22.5)        | 7 (38.9)        |
| tenofovir                                       | 15 (37.5)       | 17 (94.4)       |
| AST (IU/L)                                      | 31.3 (13.0)     | 48.2 (51.6)     |
| ALT (IU/L)                                      | 41.3 (21.6)     | 57.4 (52.3)     |
| Proteins (g/dL)                                 | 7.5 (0.5)       | 6.5 (2.5)       |
| Albumin (g/dL)                                  | 4.4 (0.8)       | 4.1 (1.1)       |
| CD4+ T cell count (cels/mm³)                    | 566 (245)       | 624 (269)       |
| HIV-1 RNA <50 copies/mL                         | 32 (80.0)       | 18 (100)        |

AST, aspartate aminotransferase; ALT, alanine aminotransferase; HBV, hepatitis B virus (measured as the presence of viral surface antigen); HCV, hepatitis C virus; NVP, nevirapine; bid, twice daily; qd, once daily.

Data are expressed as mean (SD) except when noted.

†n (%)
3.0 mg/L was 0.5%, 5.1% and 22.6% when nevirapine was dosed at 200 mg twice daily to individuals weighing 50, 70 or 90 kg, respectively, compared with 6.6%, 23.5% and 49.2% when nevirapine was dosed at 400 mg once daily to individuals weighing 50, 70 or 90 kg (\(P<0.01\)), respectively.

Discussion

A population pharmacokinetic model for nevirapine was developed and validated in the present study. Our major findings were: (i) the increase in nevirapine V/F and CL/F as body weight increases; and (ii) the higher risk of showing nevirapine trough concentrations <3.0 mg/L with once- rather than twice-daily dosing regimens, particularly in patients weighing >70 kg.

Our results are consistent with previous descriptions of the pharmacokinetics of nevirapine.\(^{22-25}\) The model that best described nevirapine behaviour was a mono-compartmental model with first-order absorption and elimination, and estimates of the pharmacokinetic parameters were in agreement with values published in the previously cited studies. However, the inter-individual variability in the absorption rate constant (\(k_a\)) in our study was greater than that reported previously.\(^{22,24,25}\) This finding can be explained by the fact that no blood samples were drawn until an hour after nevirapine administration, precluding proper estimation of \(k_a\). Body weight was the only covariate that was significantly related to the pharmacokinetic parameters of nevirapine in our study. Both CL/F and V/F of nevirapine increased, by 0.4 L/h and 13.7 L, respectively, with body weight increases of 10 kg. In contrast, we did not find any relationship between nevirapine pharmacokinetic parameters and other covariates previously described by other authors, such as gender, HCV co-infection or elevated liver enzyme levels.\(^{22-25}\) Although women showed a 14% lower nevirapine CL/F than did men in the model developed by Kappelhoff \textit{et al.},\(^{23}\) this relationship was not confirmed by the present or other studies.\(^{22,24}\) Similarly, we did not observe a relationship between HCV co-infection or abnormal liver enzyme levels and nevirapine CL/F, probably because only three participants in our study were co-infected with HCV.

As mentioned above, the possible mis-specification of the absorption phase potentially represented a source of bias in this study, resulting in an overestimation of the variability associated

Table 2. Final parameter estimates of the basic and final pharmacokinetic models

<table>
<thead>
<tr>
<th></th>
<th>Basic model estimate</th>
<th>RSE (%)</th>
<th>Final model estimate</th>
<th>RSE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL/F (L/h)</td>
<td>2.85</td>
<td>4.8</td>
<td>2.95(^a)</td>
<td>4.0</td>
</tr>
<tr>
<td>V/F (L)</td>
<td>87.5</td>
<td>7.5</td>
<td>95.2(^a)</td>
<td>6.5</td>
</tr>
<tr>
<td>(k_a) (h(^{-1}))</td>
<td>1.67</td>
<td>22</td>
<td>1.8</td>
<td>22</td>
</tr>
<tr>
<td>Inter-individual variability CL/F (%)</td>
<td>29</td>
<td>20</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>Inter-individual variability V/F (%)</td>
<td>36</td>
<td>35</td>
<td>30</td>
<td>42</td>
</tr>
<tr>
<td>Inter-individual variability (k_a) (%)</td>
<td>90</td>
<td>41</td>
<td>96</td>
<td>41</td>
</tr>
<tr>
<td>Residual error (%)</td>
<td>8.9</td>
<td>16</td>
<td>8.4</td>
<td>16</td>
</tr>
</tbody>
</table>

CL/F, oral clearance; V/F, apparent volume of distribution; \(k_a\), absorption rate constant; BW, body weight; RSE, relative standard error (as calculated with the COVARIANCE option of NONMEM).

Final pharmacokinetic models: CL/F = \(\theta_1 + \theta_2\times BW\); V/F = \(\theta_1 + \theta_2\times BW\); \(k_a = \theta_3\).

\(^a\)Expressed for an individual weighing 70 kg.
Population pharmacokinetics of nevirapine

Table 3. Summary of the models used in NONMEM to examine the influence of patients’ covariates selected by GAM analysis on nevirapine pharmacokinetics

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Model</th>
<th>$\theta_a$</th>
<th>$\theta_b$</th>
<th>$\Delta$OF</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does AGE influence CL?</td>
<td>$CL = \theta_a - (\theta_b \cdot AGE)$</td>
<td>3.97</td>
<td>0.02</td>
<td>-3.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Does BW influence CL?</td>
<td>$CL = \theta_a + \theta_b \cdot BW$</td>
<td>0.04</td>
<td>0.04</td>
<td>-36.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Does ALT influence CL?</td>
<td>$CL = \theta_a \cdot e^{(\theta_b \cdot ALT)}$</td>
<td>2.91</td>
<td>3.7 x 10^{-10}</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Does ALB influence CL?</td>
<td>$CL = \theta_a \cdot e^{(\theta_b \cdot ALB)}$</td>
<td>6.3</td>
<td>0.17</td>
<td>-4.0</td>
<td>0.05</td>
</tr>
<tr>
<td>Does BW influence V?</td>
<td>$V = \theta_a + \theta_b \cdot BW$</td>
<td>0.04</td>
<td>1.36</td>
<td>-9.9</td>
<td>NS</td>
</tr>
<tr>
<td>Does ALB influence V?</td>
<td>$V = \theta_a - (\theta_b \cdot ALB)$</td>
<td>156</td>
<td>14.9</td>
<td>-0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Does BW influence $k_a$?</td>
<td>$k_a = \theta_a \cdot BW$</td>
<td>0.03</td>
<td>2.1</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

$\theta_a$, typical value for the parameter; $\theta_b$, factor associated with the covariate; $\Delta$OF, difference in the NONMEM objective function compared with the basic structural model including no covariates; AGE, age (years); BW, body weight (kg); ALT, alanine transferase (IU/L); ALB, albumin (g/dL); $k_a$, absorption rate constant; NS, not significant.

with other parameters in the model or in a higher residual error, which might finally affect the concentration–time profile predicted by the model. Thus, the potential applicability of our model in clinical practice made the validation step of particular importance. The model correctly identified all the participating patients whose nevirapine trough concentrations were $<3$ mg/L, and only misclassified $<5\%$ of the patients who actually had nevirapine trough concentrations $>3$ mg/L. Moreover, it predicted nevirapine concentrations appropriately in an external set of patients who were not included during the model-building step, without evidence of systematic bias in individual model predictions. However, the abovementioned limitation regarding the low frequency of HCV co-infected patients in our study as well as the applicability of our results to other populations who might differ in genetic variants of the isoenzymes involved in nevirapine distribution and metabolism should be considered.

Antiretroviral treatment failure is a complex phenomenon in which several factors may play a role. Treatment adherence is crucial for attaining sustained viral suppression, and once-daily administration of antiretroviral agents to improve treatment convenience is becoming more widely used. Besides, the importance of maintaining drug concentrations high enough to
effectively suppress viral replication during the entire dosing interval has been pointed out in several studies.\textsuperscript{14,26–28} Although nevirapine was originally designed for twice-daily administration, its long plasma half-life has suggested the possibility of once-daily dosing. However, potential benefits derived from once- instead of twice-daily administration may be tempered by pharmacokinetic issues. Consistent with the findings of van Heeswijk \textit{et al.},\textsuperscript{6} estimates of nevirapine trough concentrations predicted using a population pharmacokinetic approach in our study were significantly lower when nevirapine was administered once instead of twice daily. Moreover, nevirapine trough concentrations were $<3.0$ mg/L in nearly half of the patients when body weight was 90 kg and nevirapine was given once daily. These nevirapine concentrations may be considered subtherapeutic,\textsuperscript{9} suggesting that twice- instead of once-daily nevirapine dosing would be more appropriate in this group of patients. Although the clinical relevance of this cut-off in nevirapine trough concentration has been questioned, and the sensitivity of this value was too low to be an adequate predictor for virological failure.

**Figure 3.** Goodness-of-fit plots of the validation model for nevirapine. The thick grey line is the smooth of the observed concentrations, and the thin black line is the line of identity.

**Figure 4.** Steady-state nevirapine (NVP) concentrations predicted after receiving NVP at a 400 mg once-daily (left-hand panels) or at a 200 mg twice-daily (right-hand panels) dosing regimen for patients weighing 50, 70 or 90 kg. The mean population prediction (continuous line) and the 90\% prediction interval (grey area) are represented for each category. The broken horizontal line is at an ordinate value of 3.0 mg/L.
Population pharmacokinetics of nevirapine

in the study by Leth et al.,\textsuperscript{10} there does seem to be a higher risk of virological failure in the presence of low nevirapine concentrations according to the findings of that study and other studies.\textsuperscript{7,8,14}

In conclusion, a population model to describe the pharmacokinetics of nevirapine was developed and validated in HIV-infected patients. Both nevirapine CL/F and V/F were found to be influenced by body weight, which decreased inter-individual variability in these parameters. Based on these results, twice-instead of once-daily administration of nevirapine seems to be more advisable for patients weighing >70 kg.

Acknowledgements

We thank staff at the clinical sites that collaborated in this study and the patients who participated. We wish to acknowledge the contribution of Mary Ellen Kerans who gave her assistance with English language expression in the final version of the manuscript.

Funding

The study was supported by a grant from ‘Lluita Contra La SIDA’ Foundation and by the Spanish AIDS network ‘Red Temática Cooperativa de Investigación en SIDA’ (RD06/0006).

Transparency declarations

J. Molto received honoraria for speaking engagements and participating on advisory boards from Abbott, Bristol-Myers Squibb, Boehringer-Ingelheim, Gilead Sciences, GlaxoSmithKline, Pfizer and Roche. M. V. is supported by FIS trough grant CP04/00121 from the Spanish Health Department in collaboration with Institut de Recerca de l’Hospital de la Santa Creu i Sant Pau, Barcelona, and is a member of CIBERSAM (supported by the Spanish Ministry of Health, Carlos III Health Institute). J. R. S. is supported by the Fundació Lluita contra la SIDA from Hospital Germans Trias i Pujol, Badalona. E. N. received honoraria for speaking and participation on advisory boards from Abbott, Bristol-Myers Squibb, Boehringer-Ingelheim, Gilead Sciences, GlaxoSmithKline, Pfizer and Roche. B. C. received honoraria for speaking and participation on advisory boards from Abbott, Bristol-Myers Squibb, Boehringer-Ingelheim, Gilead Sciences, GlaxoSmithKline, Pfizer and Roche. The rest of the authors have had no conflicts to declare during the course of this study.

References


