Nevirapine pharmacokinetics in HIV-infected and HIV/HCV-coinfected individuals

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Objectives: An increased risk of drug-related liver injury has been repeatedly reported in individuals infected with hepatitis C virus (HCV) receiving the antiretroviral drug nevirapine. This study was undertaken to assess the differences in the pharmacokinetics of nevirapine between patients with HIV/HCV coinfection and HIV infection that could explain higher rates of hepatotoxicity.

Methods: A 12 h pharmacokinetic analysis was performed in 18 patients: 7 HIV/HCV-coinfected and 11 HIV-monoinfected. Advanced liver disease was an exclusion criterion in order to assess the impact of chronic HCV infection alone.

Results: Comparing the two groups, no difference was observed between minimum and maximum drug levels or total drug exposure in terms of area under the curve.

Conclusions: Hepatitis C coinfection does not alter the pharmacokinetics of nevirapine in patients with preserved liver function.

Keywords: AUC, therapeutic drug monitoring, hepatitis

Introduction

Increased drug levels in patients with hepatitis coinfection have been repeatedly discussed as the underlying causes for an increased risk of nevirapine-related liver injury. Whereas several trials have addressed this issue and correlated hepatitis coinfection status and/or degree of hepatic insufficiency to random nevirapine drug levels, up to now no data on complete pharmacokinetic analysis exist.1–4 In the current study, we thus performed a complete 12 h pharmacokinetic analysis in order to investigate the differences in the nevirapine metabolism of HIV/hepatitis C virus (HCV)-coinfected and HIV-monoinfected patients.

Methods

Patients

HIV-monoinfected or HIV/HCV-coinfected patients who were on a stable nevirapine-containing highly active antiretroviral therapy (HAART) for more than 4 weeks were included. Nevirapine was dosed at 200 mg twice daily for all subjects. Liver disease other than chronic HCV had to be ruled out. Advanced liver disease was excluded by a normal ultrasound of the liver and spleen within the past 3 months. Moreover, laboratory and clinical assessment for Child–Pugh score had to be 5 points (lowest possible value). Patients were excluded in case of active AIDS-defining or other severe illness, gastrointestinal malabsorption, known or suspected non-adherence to HAART, or taking any co-medication influencing nevirapine pharmacokinetics.

All participants were admitted to our day clinic for a 12 h pharmacokinetic study. After a first blood withdrawal in a fasting state, a standardized breakfast (610 kcal; 16% protein/33% fat/51% carbohydrates) together with one tablet of 200 mg of nevirapine was taken, and consecutive blood withdrawals for pharmacokinetic sampling were taken at 1, 2, 4, 6 and 12 h thereafter. All participants had given prior written informed consent. The study was approved by the local Ethics Committee and was conducted in agreement with good clinical practice and the declaration of Helsinki and its subsequent revisions.
Nevirapine pharmacokinetics

All standard laboratory tests were performed at the Bonn University Department of Clinical Chemistry and the Institute of Microbiology and Immunology within the clinical routine. Nevirapine plasma levels were determined via a validated gas chromatography/mass spectrometry (GC/MS) method. Briefly, after the precipitation of proteins with acetonitrile, the organic phase was extracted with dichloromethane. For the determination and quantification of nevirapine, 1 µL of the organic phase was injected into the GC/MS system (GAS Chromatograph, Fisons GC 8065 and mass spectrometer, Fisons MD 800; Thermo Fisher Scientific Inc., Waltham, MA, USA). Linear calibration curves were obtained with BIRH 0414BS as an internal standard in a dynamic range from 0.01 to 15 µg/mL. Extraction efficacy from 500 µL of human plasma spiked with 4 µg/mL nevirapine was 98%. Across four different concentrations of nevirapine (1, 2, 5 and 7 µg/mL), intra- and inter-day accuracy and precision were 96% to 109% and 1.7% to 5.2%, respectively. Plasma concentrations versus time were analysed under the assumption of a non-compartmental pharmacokinetic model and steady-state conditions with oral intake of 200 mg of nevirapine every 12 h.

The highest nevirapine plasma concentration was defined as $C_{\text{max}}$ with the corresponding timepoint $T_{\text{max}}$. Correspondingly, the lowest nevirapine plasma concentration was defined as $C_{\text{min}}$ with the corresponding timepoint $T_{\text{min}}$. The area under the curve (AUC) was calculated using pharmacokinetic software WinNonlin 5.2 (Pharsight Inc., Mountain View, CA, USA).

Statistics

Based on a previous study, the sample size of 12 patients for each arm was calculated to be sufficient in order to detect a difference of 50% of $C_{\text{max}}$ with a power of 0.7 and an alpha of 0.05. Fisher’s exact and Mann–Whitney U-test using SPSS 14.0 (SPSS Inc., Chicago, IL, USA) were used for calculation of statistical comparisons.

Results

Eighteen patients were recruited into the study: 7 patients with HIV/HCV coinfection and 11 with HIV monoinfection. Comparison of HIV/HCV-coinfected patients with HIV-monoinfected patients showed no differences with regard to general demographic parameters (Table 1). Except for significantly higher liver transaminases, HIV/HCV-coinfected patients showed comparable parameters of synthetic liver function and HIV surrogate markers to HIV-monoinfected patients.

Comparing pharmacokinetic parameters, no differences were observed comparing minimum nevirapine plasma concentrations, as well as AUC of nevirapine, between the HIV-monoinfected and HIV/HCV-coinfected patients (Table 1). Importantly, no difference was observed between the groups concerning the maximum nevirapine plasma level (Figure 1).

Discussion

Hepatitis coinfection and raised transaminases have been repeatedly shown as independent risk factors for drug-related injury under HAART. For direct drug-related hepatotoxicity, raised nevirapine plasma levels in HIV/HCV-coinfected patients or patients with advanced liver disease have been observed and held responsible for this phenomenon.

However, in our study, we were able to compare HIV-monoinfected and HIV/HCV-coinfected patients by means of a full pharmacokinetic analysis. Importantly, HIV-monoinfected and HIV/HCV-coinfected patients were comparable, with regard to liver function and degree of liver fibrosis/cirrhosis so that only the impact of chronic viral hepatitis on the pharmacokinetics of nevirapine was studied. In our analysis, no differences with respect to any of the pharmacokinetic parameters were observed. In particular, $C_{\text{max}}$, which is commonly held responsible for direct toxic effects, was not different between the two groups. Therefore,

| Table 1. Demographic and pharmacokinetic parameters of HIV-infected and HIV/HCV-coinfected patients |
|----------------------------------|----------------------------------|------------------------------|
|                                  | HIV-monoinfected n=11            | HIV/HCV-coinfected n=7       | $P$ value |
| Male/female                      | 9/2 (82/18)                     | 6/1 (86/14)                 | 1.000     |
| Age (years)                      | 36 (25–51)                      | 44 (29–53)                  | 0.315     |
| Body weight (kg)                 | 74 (59–89)                      | 78 (52–106)                 | 0.643     |
| Body length (cm)                 | 178 (168–187)                   | 171 (156–187)               | 0.272     |
| CD4 cells/mm³                    | 460 (250–995)                   | 299 (172–685)               | 0.106     |
| HIV-RNA <50 copies/mL            | 8/10 (80)                       | 5/6 (83)                    | 1.000     |
| HCV-RNA (log₁₀ IU/mL)            | —                              | 6.2 (5.1–6.9)               | —         |
| ALT (IU/L)*                      | 30 (12–70)                      | 55 (43–95)                  | 0.007     |
| INR                              | 1.1 (1.0–1.2)                   | 1.0 (0.9–1.2)               | 0.209     |
| Bilirubin (mg/dL)                | 0.4 (0.2–0.7)                   | 0.5 (0.4–1.3)               | 0.093     |
| Albumin (g/L)                    | 48 (44–53)                      | 45 (42–50)                  | 0.073     |
| Platelets (G/L)                  | 211 (109–316)                   | 180 (117–228)               | 0.216     |
| $C_{\text{min}}$ (µg/mL)         | 5.97 (3.40–10.94)               | 5.69 (3.07–9.80)            | 0.821     |
| $C_{\text{max}}$ (µg/mL)         | 10.35 (6.10–19.41)              | 9.68 (2.20–13.06)           | 0.821     |
| AUC$_{0–12}$ (µg-h/mL)           | 91.86 (53.03–165.00)            | 91.53 (21.86–122.21)        | 0.892     |

Values are given as number of patients (%) or as median (range).

ALT, alanine aminotransferase; INR, international normalized ratio; $C_{\text{min}}$, minimum concentration of nevirapine; $C_{\text{max}}$, maximum concentration of nevirapine; AUC$_{0–12}$, area under the curve over the observed 12 h dosing interval.

*ALT values are shown in italics as ALT was significantly higher in HIV/HCV-coinfected patients compared with HIV-monoinfected patients.
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Figure 1. Nevirapine plasma concentrations at steady state. Plasma concentrations at the respective timepoints after a morning dose of 200 mg of nevirapine. Open circles, individual values of HIV-monoinfected patients (broken line, corresponding means of HIV-monoinfected patients); filled circles, individual values of HIV/HCV-coinfected patients (continuous line, corresponding means of HIV/HCV-coinfected patients).

other factors, not related to different pharmacokinetics, appear to be responsible for an increased risk of liver damage in HIV/HCV-coinfected patients. Recently, it has been suggested that concurrent viral infections may aggravate drug-induced liver injury by activating the hepatic innate immune system to produce proapoptotic factors. Apart from this, HCV coinfection may have served as a surrogate marker for liver insufficiency in older studies. HCV infection in HIV-infected patients takes a more rapid course and leads more quickly to advanced liver fibrosis and cirrhosis than in the HIV-negative population and is thus increasing in prevalence among HIV/HCV-coinfected patients. Indeed, newer studies show that liver fibrosis and cirrhosis, but not chronic hepatitis per se, are associated with higher risk for antiretroviral-drug-associated liver injury.

Observed pharmacokinetic data were within the range of previously published data, which report median (inter-quartile range) of: \( C_{\text{min}} \) 3.7 µg/mL (3.2–5.1); and \( C_{\text{max}} \) 5.7 µg/mL (5.0–7.4). However, one subject presented with very low \( C_{\text{min}} \) concentrations, and moreover had a detectable viral load despite being on HAART for more than 1 year. Despite our protocol and thorough interview of participants regarding their adherence, with this patient we may have included a non-adherent candidate in error. After exclusion of this patient, our analysis on comparison between nevirapine plasma levels, chronic hepatitis C infection as a possible cause for direct drug-related liver injury. As previous studies have shown, caution may be warranted, however, in patients with advanced liver fibrosis or cirrhosis.

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Transparency declarations
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