Therapeutic Drug Monitoring of Indinavir in HIV-Infected Patients Undergoing HAART

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Abstract

Background: Therapeutic drug monitoring (TDM) of protease inhibitors (PI) is gaining increasing importance for the management of HIV-infected patients undergoing highly active antiretroviral therapy (HAART). The PI indinavir (IDV) is widely used in HAART regimens. Combinations of IDV with ritonavir (RTV) have been used to increase the plasma concentration of IDV. However, the desirable IDV concentration range in clinical practice remains to be elucidated.

Patients and Methods: To study the value of TDM for IDV in clinical practice, a retrospective analysis of 501 plasma samples of patients treated with IDV in various dosages was performed. IDV levels were determined during routine outpatient visits. Analysis was performed by high pressure liquid chromatography (HPLC) with UV detection.

Results: A widespread range of IDV plasma concentrations was seen both within and between patients. The mean IDV level during therapy with IDV 2.4 g/d was 3,260 ng/ml (95% CI: 2,903 ng/ml; 3,618 ng/ml). IDV levels at a dose of IDV 1.6 g/d in combination with RTV resulted in a mean IDV plasma concentration of 4,191 ng/ml (95% CI: 3,356 ng/ml; 5,026 ng/ml). There was no significant difference between plasma levels at the doses of 2.4 g/d and 1.6 g/d. 35 of all 130 patients treated with IDV reached only suboptimal IDV plasma concentrations below the limit of 150 ng/ml. There was no statistically significant difference between the number of patients below an IDV plasma concentration of 150 ng/ml in the various dosage regimens.

Conclusion: During therapy with IDV in a b.i.d. scheme, similar IDV plasma concentrations and a comparable number of patients with subinhibitory plasma concentrations were observed when compared to a therapeutic regimen with t.i.d. dosing. In this study, even at various times of plasma sampling after oral ingestion, TCM facilitated the surveillance of patients compliance.

Key Words

HIV · Indinavir · Ritonavir · Therapeutic drug monitoring

Introduction

Although the introduction of protease inhibitors (PI) as a component of antiretroviral therapy dramatically decreased mortality and morbidity due to HIV infection, we must remember that only about 50% of patients commencing treatment will actually achieve maximal HIV suppression [1, 2].

For the long-term efficiency of highly active antiretroviral therapy (HAART) in patients with HIV infection, it is essential to achieve effective antiretroviral drug plasma levels [3, 4]. Indinavir (IDV) is widely used as an HIV protease inhibitor. Due to limited bioavailability IDV should be taken without food three times a day (t.i.d.). This leads to adherence problems in patients treated with IDV [5]. Loss of viral suppression may be due to suboptimal antiviral potency and selection of an IDV-resistant virus population [6]. Ritonavir (RTV) is a potent inhibitor of the cytochrome p450 isoenzyme 3A4 (CYP3A4) and is therefore commonly used to augment PI plasma levels [7–9]. IDV is being studied as a twice daily regimen (b.i.d.) with RTV as a way to alleviate tolerability and patient adherence [10].

Despite the lack of prospective clinical trials for the evaluation of benefits and indications of therapeutic drug monitoring, national treatment guidelines have incorporated therapeutic drug monitoring (TDM) as an option for the management of HIV infection [11].

Although IDV is widely used, the optimal range of IDV trough plasma level still remains controversial [3–5, 11]. The results of a retrospective analysis of IDV plasma concentrations from HIV-infected patients at different clinical stages treated with IDV are reported here. Plasma drug concentrations of IDV were determined in patients undergoing therapy with nucleoside reverse-transcriptase in-
hbitors (NRTI) and IDV alone, or in combination with IDV+RTV.

Patients and Methods

In this study, 123 patients were treated with IDV at different clinical stages of their HIV infection since 1996. The CDC stage was A in 35 patients, B in 62 patients and C in 26 patients, respectively. Blood sampling was performed during regular outpatient visits, not in a pharmacological study design. TDM was performed at least twice for every patient. (mean 6.6 samples; range 2–18 samples) during a mean observation time of 10 months (range 2–41 months). Determination of plasma drug concentration was performed routinely, especially in cases of ineffectiveness of HAART, assumed compliance problems or adverse events of IDV. The time between oral ingestion of the last dose and blood sampling could not always be determined, but the majority of patients took their medication in the evening before or 4 to 5 h before blood sampling. Measured plasma concentrations can therefore be assumed to be near the trough or even near a low level.

High pressure liquid chromatography (HPLC) method was used for the determination of IDV in human plasma. Quantitative recovery following liquid/liquid extraction with diethyl ether from 500 µl of human plasma was achieved. 

The HPLC system consisted of a Beckman System Gold (Beckman Instruments, Munich, Germany), a 126 solvent pump module and a 502 e autoinjector. A 167 programmable detector module and Beckman System Gold software were employed for peak determination and peak identification/integration, respectively. 

The sample preparation was performed with 500 µl of patient plasma, an equal volume of carbonate buffer (0.1M sodium carbonate/sodium bicarbonate pH 9.4) and 100 µl of an internal standard (A-86093) added to a 15 ml glass tube. The sample was vortexed for 10 s and extracted twice with 3 ml diethyl ether for 5 min, followed by centrifugation at 3,000 g (4 °C). Subsequently, the organic layers were transferred into a glass centrifuge tube and evaporated to dryness with a gentle stream of nitrogen at 37 °C.

The residue was reconstituted in 300 µl 67 mM potassium dihydrogenphosphate/methanol (1:1 v/v) and washed for 5 min with 1.5 ml n-hexane. The aqueous layer was transferred to autosampler vials with glass micro inserts for HPLC analysis. A 100 µl aliquot was injected into the chromatograph.

Subsequently, the assay was performed with a linear gradient starting at 67 mM potassium dihydrogenphosphate/acetonitrile 65 : 35 (v/v) to 40 : 60 (v/v) as a mobile phase, a Phenomenex C18 column and UV detection at 258 nm. Linear standard curves were obtained for concentrations ranging from 75 to 20,000 ng/ml for IDV. The calculated intra- and inter-day coefficients of variation were below 6%. The detection limit of indinavir in plasma was determined at 2 ng/ml and the lower limit of quantitation was reached at a concentration of 75 ng/ml for indinavir [12].

A determination of IDV plasma concentrations in different dosages of IDV 0.6 g/d (n = 17 samples), 0.8 g/d (n = 21 samples), 1.6 g/d (n = 102 samples) and 2.4 g/d (n = 344) samples was performed at various intervals after oral ingestion. The range of IDV plasma level was expressed as mean ± SD and mean ± 95% CI.

Comparison of monitored drug levels with the twofold IC 95, according to assumption of optimal trough plasma levels in the VI-RADAPT study, was done for the different dosage regimens [13].

IDV plasma levels and IC95 data were compared using the one-way ANOVA model to perform within-group comparisons. Correlation of ingested dose and IDV plasma concentration was tested with the Pearson correlation test. All statistical tests were performed at the 0.05 level of significance.

Results

In total, 484 plasma samples from 123 patients were analyzed. The mean IDV concentration was 3,330 ± 3,534 ng/ml.

Therapy with the commonly used dose of IDV 800 mg t.i.d., analyzed in 344 plasma samples of 80 patients, yielded a wide intra- and interpatient range. The mean IDV concentration was 3,260 ng/ml ± 3,385 ng/ml (95% CI: 2,903–3,618 ng/ml). During combination therapy with IDV 800 mg + RTV 200 mg b.i.d. in 102 analyzed samples of 24 patients, a mean IDV level of 4,191 ng/ml ± 4,251 ng/ml (95% CI: 3,356–5,026 ng/ml) was determined (NS). Results of TDM at various IDV dosages in combination with RTV 200 mg b.i.d. are shown in table 1. In combination with RTV there is an increase in IDV plasma levels with a strong correlation to the

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<th>Table 1</th>
<th>Indinavir plasma concentrations of 484 plasma samples from 123 patients during therapy with different dosages of IDV alone (2.4 g/d) or in combination of IDV (0.6 g/d, 0.8 g/d, 1.8 g/d) with RTV (0.4 g/d).</th>
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