J Microbiol Immunol Infect
2005;38:31-34

Dose reduction for the management of indinavir-related toxicity in human immunodeficiency virus type 1-infected patients in Taiwan: clinical and pharmacokinetic assessment

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Received: May 17, 2004 Revised: June 21, 2004 Accepted: July 30, 2004

This study evaluated the feasibility of reducing the indinavir (IDV) dosage in Taiwanese patients receiving the standard IDV/ritonavir (RTV) dosage of 800/100 mg twice a day who had undetectable plasma human immunodeficiency virus type 1 (HIV-1) RNA but had developed IDV-related toxicities. After dosage reduction to IDV/RTV 600/100 mg twice a day, the dose-related toxicity decreased and plasma HIV RNA remained undetectable at 24 weeks post-switch in all patients. The maximal plasma concentration (Cmax) and area under the plasma concentration-time curve of IDV decreased significantly (median, 6.3 vs 4.3 μg/mL and 1892 vs 1292 μg•min/mL, p=0.01 and 0.001, respectively) but the minimal plasma concentration remained at a similar level (median, 1.0 vs 0.8 μg/mL, p=0.12). This study found that the reduction in the dosage of IDV in HIV-1 infected patients receiving the standard IDV/RTV regimen guided by therapeutic drug monitoring decreased the Cmax, dose-related toxicity and medical cost without compromising viral control.

Key words: Drug toxicity, human immunodeficiency virus (HIV), indinavir, pharmacokinetics, ritonavir

The widespread use of protease inhibitor-containing regimens has produced a marked benefit in the clinical management of human immunodeficiency virus (HIV)-infected patients [1]. However, there is a marked inter-patient variability in plasma levels of protease inhibitors in patients receiving the same dose [2]. Thus, the use of so-called "standard" doses of protease inhibitors may not be suitable for all patients. To manage dose-related toxicity of protease inhibitors, dosage adjustment may be needed. However, the dose adjustment should be guided by determination of plasma levels of protease inhibitors to maintain the plasma drug levels within the appropriate therapeutic range, in order to ensure antiviral efficacy and avoid treatment failure due to a suboptimal dose [3-5].

Antiretroviral regimens consisting of dual protease inhibitors containing indinavir (IDV) and ritonavir (RTV) have been shown to be highly potent in the treatment of HIV infection [6,7] and are commonly prescribed in Taiwan. However, a small percentage of patients treated with these regimens experience toxicities which are considered secondary to high plasma levels of IDV [8]. These toxicities may impair patients' adherence to treatment and thus compromise the viral control. This pilot clinical and pharmacokinetic study evaluated the feasibility of an IDV dose reduction to IDV/RTV 600/100 mg twice a day in patients being treated with IDV/RTV 800/100 mg twice a day who had undetectable plasma HIV type 1 (HIV-1) RNA but had developed dose-related toxicity from IDV.

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Materials and Methods

From January to June 2002, HIV-1-infected, antiretroviral-naïve patients who had received an antiretroviral regimen consisting of IDV/RTV 800/100 mg twice a day for >2 months were eligible for enrollment if they experienced IDV dose-related adverse events (such as nausea, dermatoses, skin structure changes such as hair loss or paronychia, or nephrolithiasis) under adequate fluid intake (>2 liters per day). All patients signed an informed consent form prior to enrollment. The IDV dose was decreased to IDV/RTV 600/100 mg twice a day (taken with low-fat meal) while the regimens of reverse transcriptase inhibitors remained unchanged.

Follow-up including IDV-related toxicity, plasma HIV RNA, and total CD4+ T cell count was performed at 1, 4, 12 and 24 weeks after the dose reduction.

Pharmacokinetic assessment was performed before and ≥14 days after dose reduction. Blood specimens were collected pre-dose, and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 12 h post-dosing. Whole blood was collected using ethylenediamine tetra-acetic acid (EDTA)-containing tubes. Whole blood was separated by centrifugation within 10 min of blood collection, and plasma was stored at –70°C until measurement of plasma levels of protease inhibitors. Plasma levels of IDV were determined by high-performance liquid chromatography as previously described [9]. Briefly, the separation was resolved on a Luna C18 column (5 μm; 150 × 4.6 mm; Phenomenex, CA, USA) with a mobile phase of 50 mM phosphate buffer (pH 5.6): acetonitrile (55:45, v/v) at a flow rate of 1.5 mL/min. Absorbance was detected at 210 nm.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) statistical software (standard version 6.1.3; SPSS, Chicago, IL, USA). Non-parametric Wilcoxon signed rank test was used for analysis of continuous paired data. Comparison of proportions was performed by Fisher's exact test. All tests were 2-tailed and statistical significance was defined as a p value <0.05.

Results

A total of 8 eligible patients were enrolled in this study. After the time of enrollment, they had received antiretroviral therapy for a median of 24 weeks (range, 16-32 weeks). The median age of patients was 31 years (range, 25-43 years), median body height 163 cm (range, 155-170 cm), and median body weight 55 kg (range, 49-61 kg). They had normal liver function prior to the dose reduction and undetectable plasma HIV RNA (<400 copies/mL) for a median of 12 weeks (range, 4-20 weeks). The median total CD4+ T cell count was 80 cells/μL (range, 48-372 cells/μL). Two patients suffered nausea, 2 had marked dermatoses, 3 had skin structure changes (marked hair loss), and 3 had clinical evidence of nephrolithiasis (lower back pain and hematuria noted in urinalysis) despite adequate fluid intake. Hepatic function (glutamate-oxaloacetate transaminase, glutamate-pyruvate transaminase and bilirubin) and renal function (blood urea nitrogen and creatinine) of the 8 subjects were within normal range before and after IDV dosage reduction.

Following IDV dose reduction from 800 mg to 600 mg, IDV-related toxicities disappeared in all patients within 4 weeks but 1 patient developed a new episode of nephrolithiasis. Plasma HIV RNA remained undetectable at 24 weeks post-reduction in all enrolled patients. CD4+ T cell counts showed a median increase of 45 cells/μL (range, 32-98 cells/μL) during the 24-week follow-up.

Pharmacokinetic assessment revealed that the maximal plasma concentration (Cmax) of IDV decreased significantly after IDV dosage reduction (median, 6.3 vs 4.3 μg/mL, p=0.01; Fig. 1, Table 1). The area under the plasma concentration-time curve (AUC) of IDV also decreased significantly (median, 1892 vs 1292 μg•min/mL, p=0.001; Fig. 1, Table 1). However, the minimal plasma concentration (Cmin) of IDV did not show significant change (median, 1.0 vs 0.8 μg/mL, p= 0.12, Fig. 1 and Table 1). The IDV Cmin remained >0.3 μg/mL in all patients after IDV dosage reduction, which is higher than the value of IDV Cmin (0.1 μg/mL) recommended by the Department of Health and Human Services [10].

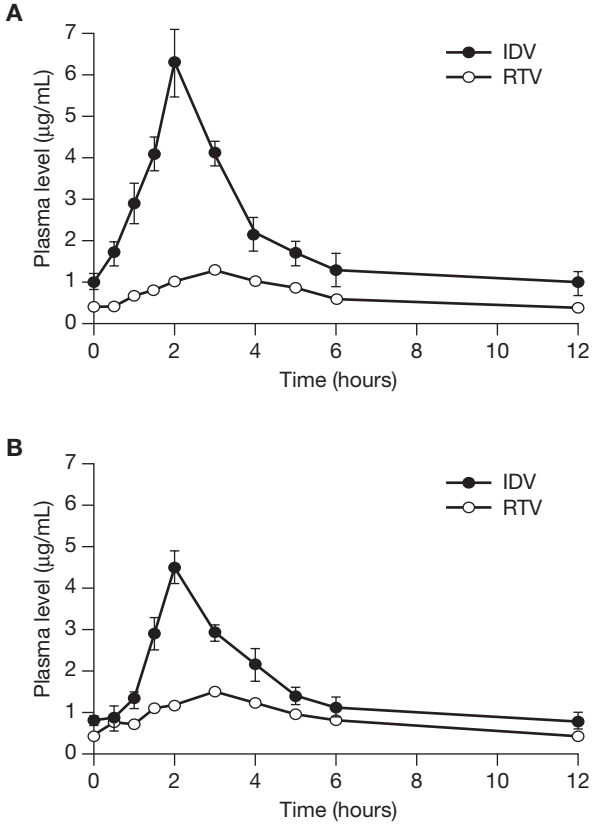

Fig. 1. Pharmacokinetics of indinavir (IDV)/ritonavir (RTV). (A) 800/100 mg twice a day and (B) 600/100 mg twice daily. Data are mean ± standard deviation.

Table 1. Pharmacokinetic data of indinavir (IDV)/ritonavir (RTV) at 800/100 mg twice daily and after reduction to 600/100 mg twice daily

	Median (range)		
	IDV Cmax (μg/mL)	IDV Cmin (μg/mL)	IDV AUC (μg•min/mL)
IDV/RTV 800/100 mg twice daily (n = 8)	6.3[a] (4.8-8.6)	1.0[b] (0.3-1.8)	1892[c] (1323-2954)
IDV/RTV 600/100 mg twice daily (n = 8)	4.3[a] (3.2-4.8)	0.8[b] (0.3-1.7)	1292[c] (988-1821)

Abbreviations: Cmax = maximal plasma concentration; Cmin = minimal plasma concentration; AUC = area under the plasma concentration-time curve

[a]p=0.01.

[b]p=0.12.

[c]p=0.001.

The IDV Cmax and Cmin of the patient who developed nephrolithiasis after dose reduction was 4.2 and 0.39 μg/mL, respectively. He was a 30-year-old man with a body weight of 57 kg. His hepatic and renal functions were normal. Family history revealed that his mother had a past history of nephrolithiasis.

Discussion

The results showed that reduction of the dose of protease inhibitors from IDV/RTV 800/100 mg to 600/100 mg did not substantially decrease the IDV Cmin, which may be the most appropriate pharmacokinetic parameter of antiretroviral efficacy [4]. This finding suggests that this dose reduction did not compromise viral load. However, the dose reduction markedly decreased the IDV Cmax, which may be the most appropriate pharmacokinetic parameter of dose-related toxicity [4]. Such reduction may decrease toxicity and possibly improve compliance and quality of life. Furthermore, dose reduction is associated with obvious cost reduction for antiretrovirals which is about US$50 per month per patient in Taiwan.

Up to nearly half of HIV-1 infected patients have evidence of virological failure under treatment with protease inhibitor-containing antiretroviral regimens [11]. Poor treatment adherence secondary to the development of drug-related toxicity may play an important role. Reduction of protease inhibitor doses may be an effective way to manage dose-related toxicity. However, dose reduction is also associated with a risk of suboptimal dosing which may lead to the emergence of drug-resistant viruses and treatment failure. Thus, therapeutic drug monitoring of plasma levels is needed to adjust the doses to avoid inadequate plasma levels, especially for Cmin [5]. The results of our study imply that it is possible to reduce the standard dose of protease inhibitors in patients treated with dual protease inhibitor regimens who have undectable plasma HIV RNA levels. The reduction should be guided by plasma level determination in order to decrease the Cmax and dose-related toxicity but not decrease Cmin such that viral control becomes compromised.

The marked variability in drug exposure or plasma drug levels in patients receiving the same doses of protease inhibitors may be caused by numerous factors, including genetic differences [3,4]. Variations among racial and ethic groups may also exist. However, the pharmacokinetic data of most antiretrovirals are comparatively limited in Asian populations. Thus, whether smaller than so-called "standard" or "recommended" doses of protease inhibitors established in western populations are adequate for Asian patients remains unclear.

This pilot study demonstrated that dose reduction of protease inhibitors from IDV/RTV 800/100 mg twice a day to 600/100 mg twice a day was feasible for clinical management for dose-related toxicity of IDV. Longer duration of follow-up and studies with larger numbers of cases are needed to establish a standard policy to manage dose-related toxicity of protease inhibitors and to assess the cost/benefit of routine application of therapeutic drug monitoring for this condition.

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