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Low Trough Levels of Tipranavir in a Combination Antiretroviral Therapy of Tipranavir/Ritonavir and Tenofovir Require Therapeutic Drug Monitoring

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Abstract
The new non-peptidic protease inhibitor tipranavir is used boosted with ritonavir in a 500/200 mg bid scheme. Multiple drug interactions are described for both drugs because of their different action in CYP450 3A4 and p-glycoprotein. In this retrospective analysis of 22 patients during therapy with tipranavir/ritonavir (TPV) 500mg/200mg bid, we found significantly decreased TPV-trough levels in combination with tenofovir (15.32 ± 5.22µg/ml) in comparision to TPV trough levels without tenofovir (20.21 ± 14.87 µg/ml). Therapeutic drug monitoring of TPV is recommended.

Key words: tipranavir, ritonavir, drug monitoring

Introduction

Tipranavir is a novel nonpeptidic protease inhibitor with activity against wild-type and multi-drug resistant HIV-1. In a clinical study, tipranavir/ritonavir 500mg/200mg twice daily in combination with an optimized background regimen was more effective than a ritonavir-boosted comparator PI plus an optimized background regimen [1, 12, 13]. A lower number of protease associated mutations and a greater number of active drugs in the background regimen were predictive of virologic success [1, 14]. Tipranavir is a substrate and an inducer of the cytochrome P450 3A4 isoenzyme, thus predisposed to interactions with other agents that are substrates, inducers or inhibitors of this enzyme family. Coadministration of tipranavir and ritonavir resulted in a greater than 20-fold increase in steady state TPV trough concentration. Thus, boosting of tipranavir in a dosage of TPV/RTV 500/200mg bid is recommended [2]. With RTV boost, the target concentration of 12µg/ml (20µmol) was reached in over 95% of healthy volunteers [2] but only 21% of heavily pretreated patients in a PI combination study [3]. An unexpected drug-drug interaction was reported between enfuvirtide and tipranvair/ritonavir [4]. Therefore, therapeutic drug monitoring may be warranted to manage a patient`s medication regimen.

The aim of the present study was to describe interactions of tipranavir and other antiretroviral drugs as tenofovir, efavirenz and enfuvirtide in a clinical setting.

Methods

Tipranavir and Ritonavir plasma levels were analysed as described before [5]. N = 42 plasma-samples of 22 patients were taken at their regular outpatient visit. So various time intervals after ingestion of tipranavir/ritonavir and different combinations of antiretroviral drugs were evaluated. The combination of tipranavir/ritonavir with efavirenz was taken of n = 4 patients, n = 3 patients have taken enfuvirtide and n=9 had a combination with tenofovir. The results of tipranavir, ritonavir and efavirenz plasma levels were correlated to the time after intake of the medication. Tipranavir plasma levels were further correlated with associated plasmalevels of ritonavir. As least the effect of combination with tenofvir on tripanavir plasma levels is evaluated. All results were given by mean ± standard deviation, statistics were performed by SPSS 11.0. As level of significance F-Test ($p<0.01$) was performed.

Results

Tipranavir plasma levels of 42 samples from 22 patients receiving TPV/RTV 500/200mg were 24.18 ± 14.48µg/ml. There was a wide range of TPV levels according the time after ingestion of the last dosage. TPV trough levels (Cssmin) were 24.15 ± 15.20µg/ml. TPV peak levels were reached between 2 and 4 hours and were 36,17 ± 11,71µg/ml. The course of TPV plasma levels given in Figure 1 shows the wide interpatient variation at different points of time after ingestion.

Combination therapy of tipranavir with tenofovir 300mg/d resulted in (n = 15) tipranavir levels of 18.89 ± 9.12µg/ml vs. 27.23 ± 16.19µg/ml without tenofovir combination ($p=0,03$). In (n=18) measures of TPV trough levels in combination with tenofovir TPV concentrations were significantly decreased (15.32 ±

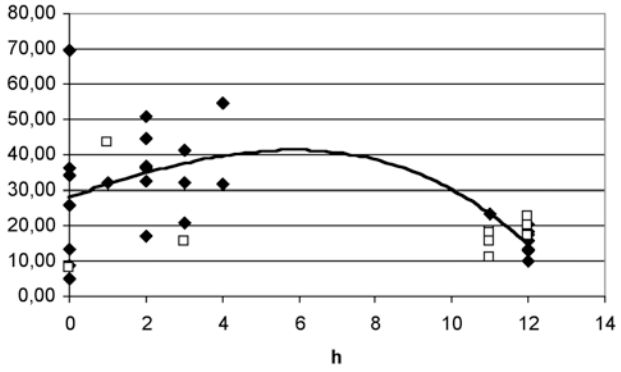

Fig. 1. Tipranavir plasma levels of n=22 patients at time after intake of TPV/rTV 500/200mg. TPV peak (Cssmax) between hour 1 and 4 is 36,17±11,71µg/ml and TPV trough (Cssmin) from hour 11to 12 is 20,21±14,87µg/ml without (_) and 15,32±5,22µg/ml in combination with tenofovir (_) (p:0,005).

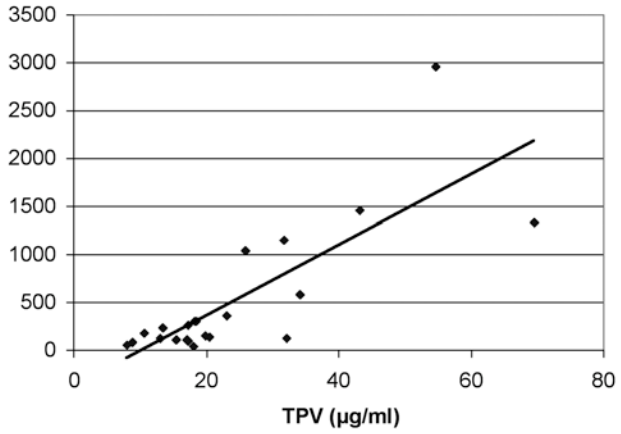

Fig. 2. Correlation of ritonavir and tipranavir plasma levels in n=22 patients. The wide interindividual range of ritonavir concentrations resulted in a mean of RTV trough (Cssmin) of 235 ± 185ng/ml.

5.22µg/ml) in comparision to TPV trough levels without tenofovir comedication (20.21 ± 14.87µg/ml) (p = 0.005). There was a wide range of tipranavir trough levels with tenofvir (7.9µg/ml to 22.3µg/ml). 3/9 TPV-levels were below 12µg/ml vs 5/18 without tenofovir comedication (range 5.2µg/ml to 69.6µg/ml) (n.s.).

Ritonavir plasma levels of all patients showed a variation between 46ng/ml and 2954ng/ml (509 ± 698.98ng/ml). There was a strong correlation between RTV and TPV plasma levels (Fig. 2). RTV trough levels were 235.13 ± 185.59ng/ml. There was no difference between RTV levels with tenofovir combination (240.67 ± 190.82ng/ml) and without tenofovir (231.44 ± 193.59ng/ml). RTV levels below 100ng/ml resulted in 2/4 patients in tipranavir levels below 12µg/ml. Thus, an ritonavir plasma level below 100ng/ml is associated with an low tipranavir concentration in 90% (negative predictive value 0.10). Only 2/15 ritonavir trough levels were over 500ng/ml and were associated with a mean tipranavir level of 24.65µg/ml.

Only 3 patients received a combination with tipranavir and enfuvirtide. Tipranavir plasma levels of these patients were 18.20 ±1 3.53µg/ml with no sign of interaction.

Tipranavir levels in combination with efavirenz were 19.45 ± 11.32µg/ml vs 27.44 ± 22.54µg/ml without the NNTRI (n.s.). The additionally analysed efavirenz levels were in the target range of 1000-4000ng/ml (2359 ± 573ng/ml).

Discussion

The pharmacokinetics of tipranavir is complex (6). An erythromycin breath test, as a marker for cytochrome P450 isoenzyme 3A4 activity, indicated that tipranavir/ritonavir combination provided net inhibition of this isoenzyme [2]. Tipranavir is a substrate and inducer of cytochrome P450 3A4 isoenzyme. Thus, TPV is predisposed to interactions with other agents that are substrates, inducers or inhibitors of this enzyme family [7]. In vitro and in vivo data suggest that tipranavir is a substrate for and an inducer of P-gp activity [8].

The presence of five or fewer protease gene mutations (PRAMS) is associated with reduced susceptibility to currently available protease inhibitors. However, 16-20 mutations may be needed to confer resistance to tipranavir. In the RESIST studies of multi-drug resistant patients, 33,6% of patients in the tipranavir group achieved maintained treatment response until week 48. [9]. The recommended dosage is tipranavir/ritonavir 500/200mg bid.

The average steady state tipranavir trough concentration is above 20 times the protein adjusted tipranavir IC90 for protease inhibitor-resistant HIV-1 strains [2]. The primary target threshould level of tipranavir is assumed to about 20µmol (12µg/ml). In the clinical setting of our retrospective study, 8/42 (19%) tipranavir levels are found to be below this target concentration. This is comparable to an other study of 190 patients receiving different tipranavir combination therapies [11]. The number of tipranavir concentrations below the target level of 12µg/ml in our study is higher but even not significant in patients receiving tenofovir comedication. The great variation and the significantly decreased mean of tipranavir levels in combination with tenofovir found in our study is a sign for interaction and not known until now. The mechanism of interaction remains unclear yet. The long list of potential interactions of tenofovir [3] should include tipranavir.

Patients with low tripranavir score and a high number of protease associated mutations will be vulnerable for insufficient drug levels in this combination [1].

Despite of the low number of patients and the problem of not full pharmacokinetic screening of the patients, every point of measurement is representative for the potency of drug concentration in the patient. So the finding of a high percentage of insufficent dug levels should be a strong link to therapeutic drug monitoring in salvage patients.

The small group of patients receiving enfuvirtide comedication in our study showed not unexpected high tipranavir plasma levels as stated in an other com-

munication [4]. If high tenofovir and/or high associated ritonavir concentrations are the reason of especially severe hepatotoxicity as described [9], this problem needs further evaluation.

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