Impact of rosiglitazone treatment on the bioavailability of antiretroviral compounds in HIV-positive patients

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Objectives: The insulin-sensitizer rosiglitazone is under investigation for therapy of HIV-associated lipodystrophy syndrome (LDS). Little is known about pharmacological interactions with antiretroviral (ARV) drugs.

Methods: Therapeutic drug monitoring (TDM) of ARV drugs was performed in a prospective study before and at day 28 after start of treatment with 4 mg of rosiglitazone for combined LDS. Drug levels were measured in the morning fasting, and 0.5, 1, 2, 4, 6 and 8 h after standardized drug intake. Values were log-transformed for analysis.

Results: Twelve males and six females were assessed; mean age was 50.7 years and mean CD4 cell count was 496 cells/mm³. All patients had a viral load below 50 copies/mL, and backbone ARV therapy consisted of two or three nucleoside reverse transcriptase inhibitors in all cases. After administration of rosiglitazone, no significant differences in $C_{\text{max}}$, $C_{\text{min}}$ and AUC were found in cases treated with efavirenz ($n = 10$) and lopinavir ($n = 4$). Mean $C_{\text{max}}$ of nevirapine ($n = 4$) was reduced significantly $[-0.44; 95\% \text{ confidence interval} \ (CI) -0.86 \text{ to } -0.01]$. Furthermore, there was a consistent trend to a reduction in the geometric mean ratio (GMR) of $C_{\text{max}}$, $C_{\text{min}}$ and AUC (GMR of $C_{\text{max}} 0.95; 95\% \text{ CI} 0.90\text{–}1.00$; GMR of $C_{\text{min}} 0.89; 95\% \text{ CI} 0.65\text{–}1.13$; GMR of AUC 0.96; 95\% CI 0.91–1.01).

Conclusions: Treatment with 4 mg of rosiglitazone for HIV-associated LDS is likely to reduce the bioavailability of nevirapine. Thus, routine TDM is recommended for patients treated with rosiglitazone and nevirapine. A therapy consisting of efavirenz or lopinavir seems to be without negative impact. Further studies on the interaction of rosiglitazone with ARV drugs are necessary.

Keywords: HAART, therapeutic drug monitoring, glitazones, drug interactions

Introduction

Since the widespread use of highly active antiretroviral therapy (HAART), the morbidity and mortality of HIV infection has declined dramatically. However, the success of this treatment strategy was accompanied by a number of side-effects such as the lipodystrophy syndrome (LDS). The disorder is characterized by fat redistribution and metabolic disorders like hyperlipidaemia and reduced insulin sensitivity.¹ The prevalence of LDS varies between 18% and 70% after several years of HAART.²

Thiazolidinediones (glitazones) are currently under investigation in vivo as drugs with a potential for improving LDS. They are used as insulin sensitizers and act as stimulators of the peroxisome proliferator-activating receptor type γ (PPAR-γ), which is known to play an important role in adipocyte differentiation and insulin sensitivity.³ The adverse effect of protease inhibitors on adipocyte homeostasis can be inhibited in vitro by PPAR-γ activation.⁴ Moreover, experience in the treatment of type 2 diabetics with glitazones revealed loss of intra-abdominal fat and accumulation of subcutaneous fat as a side-effects of therapy.⁵ On the basis of these facts, the glitazone rosiglitazone was studied in the treatment of HIV-associated LDS. Several trials produced contradictory results regarding insulin sensitivity and body fat distribution.⁶,⁷ Rosiglitazone is metabolized predominantly by the cytochromes P450, 2C8 and, to a lesser extent, 2C9 in the liver, which are inhibited by rosiglitazone in a moderate way.⁸ Recent in vitro

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studies showed a dose-dependent induction of 3A4, an important enzyme for drug metabolism of antiretroviral compounds. Thus, there is a potential of drug interaction with non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) as components of HAART. We studied the impact of rosiglitazone therapy on the bioavailability of NNRTIs and PIs in HIV patients suffering from LDS.

Methods

In an open-label prospective trial in the outpatient unit of a university clinic, therapeutic drug monitoring (TDM) of NNRTIs and PIs within a stable HAART before and after rosiglitazone treatment introduction was performed. The study received approval by the local institutional review board (ethics committee of the University Clinic of Düsseldorf, Germany). Inclusion criteria were documented HIV infection, informed consent, and the presence of combined LDS as diagnosed by patient’s self-report, clinical examination and computed tomography of the abdomen. Furthermore, patients had to be on antiretroviral treatment for more than 6 months. Exclusion criteria were lack of informed consent, AIDS-defining disease, malignant disorder, chronic hepatitis B or C co-infection, grade 3 and 4 laboratory abnormalities, concurrent drug abuse, pregnancy, and co-medication with insulin, steroids, non-steroidal anti-inflammatory drugs or growth hormone.

Patients presented on day 0 and day 28 of rosiglitazone treatment for TDM. Blood samples were drawn in the morning fasting, and 0.5, 1, 2, 4, 6 and 8 h after drug intake with breakfast in patients on nevirapine and lopinavir therapy. Concerning cases treated with efavirenz, the same schedule was carried out with the difference of the patient having taken their regular dose the night before. Plasma concentrations were measured using a validated HPLC tandem mass spectrometry method. Pharmacokinetic parameters were assessed using non-compartmental analysis. Maximum (C_{max}) and minimum (C_{min}) concentration values, as well as calculation of the AUC over the period of 8 h (AUC_{0–8} for lopinavir and nevirapine and AUC_{10–18} for efavirenz) using the linear trapezoidal rule were determined for each patient on day 0 and day 28 of rosiglitazone treatment. Ritonavir concentrations were not included in the analysis because this compound is used as a booster of lopinavir.

Pharmacokinetic parameters were log-transformed before statistical analysis. Mean steady-state C_{max}, C_{min} and AUC on day 28 were compared with mean values on day 0 [including 95% confidence intervals (CIs)] using the Wilcoxon rank sum test. Furthermore, a geometric mean ratio (including CI) was calculated for each parameter. Differences were considered statistically significant if the P value was <0.05 or CI did not include unity. Statistical analysis was performed with the help of SPSS, release 12.0.

Results

A total of 18 patients entered the study between January 2002 and February 2003 after informed consent was obtained. Baseline parameters were as follows. Twelve of the cases were males (66.7%) and six were females (33.3%). Mean age was 50.7 years [standard deviation (SD) 8.6], mean duration of HIV diagnosis was 8.7 years (SD 4.0) and mean body mass index was 24.2 kg/m² (SD 3.2). Six patients were at CDC stage A of HIV infection (33.3%), four at stage B (22.2%) and eight at stage C (44.4%). Mean CD4 count was 496 cells/mm³ (SD 277) and all patients had a viral load <50 copies/mL.

Pharmacological data were available for 10 subjects on efavirenz-based therapy, four subjects receiving nevirapine and four subjects

<table>
<thead>
<tr>
<th>Substance</th>
<th>C_{max} difference (95% CI; P-value)</th>
<th>GMR (95% CI)</th>
<th>C_{min} difference (95% CI; P-value)</th>
<th>GMR (95% CI)</th>
<th>AUC difference (95% CI; P-value)</th>
<th>GMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>-0.09 (-0.24 to 0.06; 0.20)</td>
<td>0.99 (0.97 to 1.01)</td>
<td>-0.02 (-0.34 to 0.31; 0.88)</td>
<td>0.99 (0.95 to 1.05)</td>
<td>-0.07 (-0.27 to 0.14; 0.51)</td>
<td>0.99 (0.97 to 1.02)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>-0.44 (-0.86 to -0.01; 0.07)</td>
<td>0.95 (0.90 to 1.00)</td>
<td>-0.84 (-2.73 to 1.05; 0.07)</td>
<td>0.89 (0.65 to 1.13)</td>
<td>-0.41 (-0.96 to 0.13; 0.07)</td>
<td>0.96 (0.91 to 1.01)</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>0.04 (-0.31 to 0.39; 0.47)</td>
<td>1.01 (0.97 to 1.05)</td>
<td>0.28 (-0.63 to 1.20; 0.47)</td>
<td>1.04 (0.91 to 1.17)</td>
<td>0.14 (-0.37 to 0.65; 0.47)</td>
<td>1.01 (0.96 to 1.06)</td>
</tr>
</tbody>
</table>
receiving ritonavir-boosted lopinavir. All patients received the drug at standard dosage (efavirenz, 600 mg once a day; lopinavir/ritonavir, 400/100 mg twice a day; nevirapine, 200 mg twice a day). Antiretroviral co-medication consisted of two or three NRTIs. The evolution of pharmacokinetic parameters is listed in Table 1. The bioavailability of efavirenz and lopinavir was not altered significantly. A substantial change in pharmacokinetic parameters was seen for nevirapine, with a significant reduction in $C_{\text{max}}$ and a trend to a lower AUC and $C_{\text{min}}$ that did not reach statistical significance. $C_{\text{min}}$ of nevirapine was found to be $<3400$ ng/mL on day 1 in two cases and on day 28 in all cases. The development of pharmacokinetics of this compound is shown in Figure 1.

**Discussion**

Rosiglitazone is currently under investigation in the treatment of HIV-associated LDS. Owing to potential pharmacological interaction, the impact of rosiglitazone therapy on the bioavailability of antiretroviral compounds was assessed in 18 patients suffering from combined LDS. All patients received effective HAART.

Results of TDM of different antiretroviral compounds are shown in Table 1. We found no significant difference in $C_{\text{max}}$, $C_{\text{min}}$ and AUC measurements for efavirenz and lopinavir. However, the $C_{\text{max}}$ value of nevirapine was reduced significantly considering the difference of means. Looking at the geometric mean ratio (GMR), evolution of $C_{\text{max}}$ after rosiglitazone administration almost reached statistical significance. The $C_{\text{min}}$ and AUC values were also markedly reduced, but the difference was not statistically significant. Thus, the bioavailability of nevirapine seems to be reduced by rosiglitazone co-medication. The lack of a statistically significant reduction in the differences and GMR seen for the pharmacokinetic parameters may be explained by the limited sample size, as only four patients were treated with nevirapine. The effect on nevirapine was underscored by the fact that trough levels of nevirapine were reduced below the lower threshold of 3400 ng/mL in two cases. Further studies considering more patients may help to define more clearly the influence of rosiglitazone on nevirapine bioavailability. Whereas a reduction in $C_{\text{max}}$ may not affect efficacy of antiretroviral therapy, a reduction in $C_{\text{min}}$ and AUC will be of substantial clinical importance for the patients.

Reasons for the drug interaction between rosiglitazone and nevirapine may be the interaction via liver cytochromes 3A4, 2C8 or 2C9. Nevirapine is metabolized predominantly by cytochromes 3A4 and 2B6. This may explain part of the identified effect, as nevirapine is known to be a strong inducer of 3A4. Efavirenz is both an inducer and an inhibitor of the cytochromes. The possible interactions of lopinavir and its booster ritonavir are even less predictable. However, the inhibition of cytochrome 3A4 caused by these agents does not seem to play a role in the metabolic pathways of rosiglitazone. Further impact on bioavailability of rosiglitazone may be caused by interactions on the level of efflux pumps like p-glycoprotein in the liver or intestinal mucosa. Finally, there are other important modifiers of pharmacokinetics like polymorphisms of metabolizing enzymes or concomitant disease. In conclusion, the effect of rosiglitazone on antiretroviral drugs remains poorly understood.

The results of this study may be limited by several factors. The sample size was too small to give a precise estimation of drug interaction. Only the group evaluated for efavirenz plasma levels was sufficient to state that an interaction is small. Thus, more data on the pharmacokinetic interaction of HAART compounds are required.

We determined drug levels over 8 h and thus could not calculate 12 or 24 h AUCs. This is another bias of our study, resulting in a possible loss of information. However, considering the short $t_{1/2}$ of lopinavir and nevirapine and the very long $t_{1/2}$ of efavirenz, it is unlikely that we have missed the most important changes in pharmacokinetics of these compounds. This is because the most important measurements of $C_{\text{min}}$ and $C_{\text{max}}$ of the compounds with a small $t_{1/2}$ are well within the measurement period. Moreover, in the case of efavirenz with its long $t_{1/2}$, the circadian variation of drug levels is extremely low and thus there is a low impact of the time of therapeutic drug monitoring.

In conclusion, we demonstrate an unfavourable influence of 4 mg of rosiglitazone therapy on nevirapine bioavailability in our study. We found no significant impact on plasma concentrations of efavirenz and lopinavir. Thus, TDM is necessary in cases of rosiglitazone co-medication with a nevirapine-containing HAART. Owing to the limited size of the studied population, these data should be confirmed by larger trials and different dosages of rosiglitazone treatment.

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**References**

Rosiglitazone and HAART


