MIC also increased 4-fold (from 0.06 to 0.25 mg/L), since it is a semi-synthetic derivative of the natural glycopeptide produced by a 3,3-dimethylaminopropyl amide substitution on the peptide carboxyl group. This agent is similar to other glycopeptides in its mechanism of action by binding to the terminal alanyl-D-alanine of nascent peptidoglycan chains.

Since extended use of daptomycin resulted in elevated MIC values of these glycopeptides (vancomycin and daptomycin), it is possible that exposure to daptomycin, like vancomycin, may cause thickening of the bacterial cell wall, thus decreasing susceptibility to a number of peptides. Another recent study also showed that prolonged exposure to vancomycin prior to daptomycin treatment increases the risk of emergence of a daptomycin non-susceptible subpopulation. Further studies are necessary to better understand the cell wall alterations initiated by prolonged daptomycin exposure and their effect on the activities of structurally related peptides (glycopeptide and lipoglycopeptide agents).

Finally, daptomycin seems to offer a bactericidal alternative for treatment of MRSA infections that are unresponsive to vancomycin; however, this case illustrates the adaptability of S. aureus necessitating clinicians to be aware of the possible daptomycin resistance associated with therapy following vancomycin failure.

Transparency declarations

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References


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Ritonavir-dependent fluconazole boosting of nelfinavir: a report of three cases


Department of Infectious Diseases, University of Turin, Turin, Italy

Keywords: pharmacokinetics, drug interactions, therapeutic drug monitoring

*Corresponding author. Tel: +39-333-2466363; Fax: +39-011-4393977; E-mail: silvia.garazzino@inwind.it

Sir,

The use of ritonavir-boosted dual protease inhibitor (PI) combinations is increasingly considered in HIV-infected patients with a history of multiple therapeutic failures. Although pharmacokinetic (PK) studies on several of such combinations provided valuable information on how to cope with drug–drug interactions between concurrently administered PIs, substantial uncertainty persists on the best management of double-boosted PI-based regimens. In this setting, the introduction of fluconazole as additional boosting agent was found to restore the otherwise reciprocally reduced concentrations of co-administered lopinavir/ritonavir and amprenavir, and higher PI PK exposure was also documented when fluconazole was added to ritonavir/saquinavir and ritonavir/tipranavir. In a pre-registration study it was found that in patients exposed to nelfinavir, but not to ritonavir, the addition of fluconazole resulted in a 27% reduction of nelfinavir oral clearance. Fluconazole is a weak inhibitor of CYP3A4 and a strong inhibitor of both CYP2C9 and CYP2C19. Fluconazole boosting properties on nelfinavir might be attributable primarily to the inhibitory action on CYP2C19, as the same isoenzyme is responsible for nearly 50% of nelfinavir clearance through the transformation into the nelfinavir metabolite M8. The latter is probably the major metabolic difference between nelfinavir and the other PIs, whose metabolism depends upon CYP3A4 to a greater extent, and it might account for the significant lesser sensitivity of nelfinavir to the boosting effect of ritonavir.

In the therapeutic drug monitoring (TDM) database of the Department of Clinical Infectious Diseases of the University of Torino, Italy, where TDM is carried out on a regular basis, three patients receiving both nelfinavir and fluconazole were found. In one case the antiretroviral regimen also included lopinavir/ritonavir as booster, while the other two patients were given nelfinavir and fluconazole without ritonavir. In all such cases fluconazole was introduced and administered for 4 weeks at a dosage of 100 mg twice daily in order to treat a concomitant oropharyngeal candidiasis. No co-medications were administered in the study period. Plasma samples for PK analysis were

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drawn both before introducing fluconazole and on the 28th day of fluconazole administration, at 0, 2, 4 and 12 h ($t_0$, $t_2$, $t_4$ and $t_{12}$, respectively) after the morning dose intake of drugs. On both PK days patients underwent a standard procedure and received feeding after $t_0$ and $t_4$ determinations. Plasma concentrations of nelfinavir, M8 metabolite and co-administered PIs were measured by a validated liquid chromatography mass spectrometry (LC-MS/MS) method and $C_{\text{max}}$, $C_{\text{min}}$ and AUC$_{0-12}$ were respectively determined by non-compartmental analysis using Win Nonlin Professional 4.1 (Pharsight Corporation, Mountain View, CA, USA). The PK findings of the three patients are shown in Table 1.

The first patient was a 50-year-old man who was administered an unusual liquid regimen consisting of nelfinavir 1250 mg twice daily and lopinavir/ritonavir 533.3/133.3 mg twice daily, since he was unable to swallow any tablet-based therapy. Co-administration of fluconazole led to a variable increase of all PK parameters of lopinavir, ritonavir and nelfinavir, with the noticeable exception of the nelfinavir metabolite M8, the latter reduced to barely measurable levels. The major increases were seen in nelfinavir parameters, with $C_{\text{max}}$, $C_{\text{min}}$ and AUC$_{0-12}$ values that rose to levels 2.44, 2.12 and 2.6, respectively, higher than those measured in the absence of fluconazole.

The other two patients, both males respectively aged 42 and 48 years, were treated with nelfinavir 1250 mg twice daily and stavudine 40 mg twice daily, in association with abacavir 300 mg twice daily or efavirenz 800 mg once daily, respectively. In contrast to the first patient, the introduction of fluconazole in these two patients not taking ritonavir did not cause any significant change of either nelfinavir or its M8 metabolite. It must be noted that these two patients had differences in both nelfinavir and M8 PK parameters, probably due to concomitant efavirenz (a CYP3A4 inducing drug) intake by patient 3, but no significant changes in each patient’s PK profile before and after the introduction of fluconazole were recorded. These findings question why fluconazole boosting effects were recognizable only in the presence of ritonavir. As also suggested in the analysis of the triple interaction of atazanavir, saquinavir and ritonavir, where the addition of atazanavir was associated with an otherwise unexpected rise in exposure of both saquinavir and ritonavir, some boosting synergy between fluconazole and ritonavir might have taken place at the cytochrome P450 level.$^1$ It appears possible to hypothesize that, in the absence of ritonavir, fluconazole preferentially binds to CYP3A4 (to which fluconazole might have greater affinity than to CYP2C19), which results in negligible variations of nelfinavir PK exposure; in contrast, in the case of co-administration of ritonavir, the latter’s affinity for CYP3A4 might be greater than that of fluconazole to supersede fluconazole binding to CYP3A4, thus driving fluconazole towards a greater interaction with CYP2C19, whose inhibition accounts for the rise in nelfinavir exposure and reduction of M8 metabolite. Since M8 results from nelfinavir biotransformation by CYP2C19, the significant reduction in M8 concentration following fluconazole introduction in the patient also taking ritonavir provides further support to this interpretation.

Although these findings were derived from the study of only three patients, they nevertheless provide the basis for further investigation of fluconazole as a possible additional boosting agent for nelfinavir. Albeit nelfinavir is no longer included among the first-choice regimens for antiretroviral therapy, its rather good tolerability profile, with no proven concentration-dependent side effects, warrants further study in the light of

### Table 1. Plasma concentrations of nelfinavir, M8, ritonavir and lopinavir without (baseline) and with fluconazole co-administration in the three patients studied

<table>
<thead>
<tr>
<th>Patient 1 (NFV + LPV/RTV)</th>
<th>Patient 2 (NFV + d4T + ABV)</th>
<th>Patient 3 (NFV + d4T + EFV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>nelfinavir</td>
<td>ritonavir</td>
<td>lopinavir</td>
</tr>
<tr>
<td>Base line</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>$C_{\text{min}}$</td>
<td>AUC$_{0-12}$</td>
</tr>
<tr>
<td>63,000</td>
<td>7378</td>
<td>3769</td>
</tr>
<tr>
<td>65,103</td>
<td>6970</td>
<td>6892</td>
</tr>
</tbody>
</table>

$^a$ Plasma concentration during fluconazole intake/baseline.

$^b$h·ng/mL.

$^c$ng/mL.
possibly improving its PK exposure through ritonavir-fluconazole co-boosting. The prolonged half-life of fluconazole (31–34 h), allowing once daily administration, would add only a reasonable extra pill burden to the patients while providing a more potent antiretroviral action.

Transparency declarations

None to declare.

References


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Non-nucleoside-reverse-transcriptase-inhibitor-based HAART and osteoporosis in HIV-infected subjects

Marco Bongiovanni1*, Alfonso Fausto2, Paola Cicconi3, Alberto Alliprandi2, Giampaolo Cornalba3, Teresa Bini3, Francesco Sardanelli2 and Antonella D’Arminio Monforte1

1 Clinic of Infectious Diseases, San Paolo Hospital, University of Milan, Milan, Italy; 2 University of Milan, School of Medicine, Department of Medical and Surgical Sciences, Radiology Unit, IRCCS Policlinico di San Donato, Milan, Italy; 3 Department of Diagnostic and Interventional Radiology, San Paolo Hospital, University of Milan, Milan, Italy

Keywords: bone, NNRTIs, highly active antiretroviral therapy

*Correspondence address. Clinic of Infectious and Tropical Diseases, San Paolo Hospital, via di Rudini 8, 20142 Milano, Italy. Tel: +39-0281843061; Fax: +39-0281843054; E-mail: marco.bongiovanni@unimi.it

SIR,

A significant improvement of survival of people infected with HIV has been observed since the introduction of HAART in clinical practice.1 Several toxicities have arisen such as lipo-dystrophy, insulin resistance, diabetes, dyslipidaemia and also abnormalities of bone metabolism such as osteopenia/osteoporosis and osteonecrosis.2–4 HIV infection, a prolonged use of protease inhibitors (PIs), lactic acidosis, lipodystrophy, immune reconstitution, nutritional and hormonal factors and prior AIDS-related wasting are all factors that can contribute to these abnormalities.5,6

No data are at the moment available on the frequency and on the predictive factors of osteopenia/osteoporosis in HIV-infected subjects receiving a non-nucleoside-reverse-transcriptase-inhibitor (NNRTI)-based HAART.

This observational prospective study involved 89 consecutive HIV-infected subjects aged between 30 and 50 years: patients with pathological or toxic conditions potentially affecting bone metabolism such as hypogonadism, hyper- or hypothryoidism and hypocortisolism, bed rest period >1 month, drug/alcohol abuse, neoplasia, chronic diarrhoea or absorption dysfunction, body mass index (BMI) < or >20% normal ranges (19.1–25.8 for women and 20.7–26.4 for men), chronically treated with corticosteroids, levothyroxine, lithium or oestrogens, and women in menopause or amenorrhoea were excluded. We included in the study both naive and HAART-treated subjects. Patients receiving antiretroviral treatment were naive for PIs and were receiving a stable, first-line, NNRTI-containing HAART for at least 2 years with HIV-RNA < 50 copies/mL in the previous 6 months.

All subjects underwent dual energy X-ray absorptiometry (DEXA) scans (Hologic, QDR 4500 Delphi system, Bedford, MA, USA) in antero-posterior lumbar spine (L1-L4) and left hip sites to evaluate mean bone mineral density (BMD), total mean T-score and Z-score. DEXA were performed at the same radiological centre by a single radiologist, and WHO criteria were considered for the diagnosis of osteopenia/osteoporosis. Written informed consent was obtained from all participants, and the study was conducted in adherence with local drug regulations, guidelines on ‘Good Clinical Practice’ and the principles of the Declaration of Helsinki.

Comparisons between categorical groups were performed by χ² and Wilcoxon tests. Potential predictive factors of osteopenia/osteoporosis were evaluated by a multivariate regression logistic analysis. Variables included in the model were gender, age, risk factors for HIV infection, CDC stage, hepatitis C virus (HCV) serostatus, BMI, lipodystrophy, CD4 cell count at DEXA, months since first HIV-positive test and use of NNRTI-containing HAART. A similar analysis was repeated including only NNRTI-treated subjects to evaluate the role of NNRTI-based HAART duration in the occurrence of osteopenia/osteoporosis.

Table 1 summarizes demographic and clinical characteristics of the subjects included in the study: 47 were naive and 42 were NNRTI-treated. As expected, naive patients had a lower duration of HIV infection and a lower CD4 cell count than NNRTI-treated patients. Median duration of HAART was 41 months.