Intra-abdominal penetration and pharmacodynamic exposure to fluconazole in three liver transplant patients with deep-seated candidiasis

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Sir, Invasive candidiasis is a major cause of mortality and morbidity after liver transplantation (LTx). Immunosuppression may predispose transplant patients to infections, and in the specific context of LTx recipients the surgically reconstructed biliary tract may represent a primary site for infectious complications. It has been shown that the impairment of bile excretion, a frequent condition in LTx patients, may increase the likelihood of developing invasive fungal cholangitis. Additionally, invasive candidiasis may be commonly associated with peritonitis in these patients.

Fluconazole is presently the drug of first choice for the treatment of intra-abdominal candidiasis in those patients who are not critically ill and who have no specific risk factors or previous azole exposure.

To our knowledge, no data on intra-abdominal fluconazole exposure in LTx patients have been published. Here we report on the intra-abdominal penetration and pharmacodynamic exposure in three LTx patients who had documented intra-abdominal candidiasis (cholangitis in Patients 1 and 2; peritonitis in Patient 3) treated with fluconazole. Informed consent for bile or ascites and blood sampling was obtained from the patients. Single bile samples (from a T-tube that was used for splitting the biliary anastomosis between the donor’s and the recipient’s bile ducts) or ascites samples (during diagnostic paracentesis) and simultaneous blood samples (from the antecubital vein) were collected at steady-state just before the daily fluconazole administration for assay of trough concentrations (Cmin). Plasma, ascites and bile fluconazole concentrations were measured by means of a validated HPLC technique, with some modifications.

At the Institute of Clinical Pharmacology fluconazole dosages are routinely adjusted in real time by therapeutic drug monitoring (TDM) in LTx patients, with the intent of maintaining plasma Cmin at around 10–15 mg/L. This approach should ensure an AUC/MIC ratio of >105,6 against all fluconazole-susceptible strains of Candida (MIC ≤2 mg/L).7

Briefly, Patient 1 (60–70 years, 60–70 kg and serum creatinine 1.2 mg/dL) and Patient 2 (60–70 years, 60–70 kg and serum creatinine 1.18 mg/dL) had a diagnosis of Candida cholangitis at 14 days and 30 months post-transplant, respectively. Candida albicans strains susceptible to fluconazole (MIC 0.25 mg/L; Sensititre YeastOne colorimetric MIC procedure) were isolated from the biliary drainage of both patients. Intravenous fluconazole was started with a 400 mg loading dose, followed by TDM-guided maintenance dosages (200 mg daily reduced to 100 mg daily from day 10 for Patient 1; 200 mg daily for the whole treatment period for Patient 2). Fluconazole bile and plasma Cmin (Table 1) were 9.04 and 17.81 mg/L, respectively at therapy day 9 for Patient 1, and 6.29 and 12.61 mg/L at therapy day 5 for Patient 2.

Patient 3 (60–70 years, 60–70 kg and serum creatinine 1.7 mg/dL) developed Candida peritonitis at day 62 post-transplant, after a history of recurrent, refractory ascites. Cultures from ascites yielded C. albicans susceptible to fluconazole (MIC 0.25 mg/L; Sensititre YeastOne colorimetric MIC procedure). Intravenous fluconazole was started with a 400 mg loading dose followed by a maintenance dose of 150 mg daily, then reduced to 100 mg daily from day 8. Fluconazole Cmin in ascites and plasma at therapy day 5 was 9.60 and 11.30 mg/L, respectively (Table 2).

The fluconazole bile-to-plasma ratios of Cmin in the two LTx patients with cholangitis (0.50 and 0.51) were lower than previously observed in a non-LTx patients with Candida cholecystitis (around 1.2 at therapy day 5 by visual inspection). Conversely, the ascites-to-plasma ratio of Cmin in the LTx patient with peritonitis (0.85) was similar to that observed in a non-LTx cirrhotic patient with Candida peritonitis (0.81 at 3 h post-dose at therapy day 5).8

Interestingly, 14 days of fluconazole treatment with maintenance of plasma Cmin at around 15 mg/L resulted in clinical resolution of intra-abdominal candidiasis in all three LTx patients with no evidence of recurrence at 30 days of follow-up. It should be noticed that, thanks to TDM, in these particular patients successful treatment was based on doses of fluconazole much lower (100–200 mg/day) than those usually administered for systemic infections (400–800 mg/day).9 Previous studies showed that the AUC/MIC ratio is the pharmacodynamic parameter that best correlates with fluconazole efficacy, and the recent
guidelines from the British Society for Medical Mycology recommend a value of >100 for optimal fluconazole exposure when the MIC is tested using EUCAST methodology. Rough estimates of minimum AUC/MIC ratios of fluconazole against C. albicans isolated from bile and/or ascites (expressed as (bile or ascites C_{min}/24 h)/MIC for Candida isolate in bile or ascites) were well above this threshold (>600) in our patients.

We recognize that the absence of real AUC measurements may be a limitation, since our approach led to gross underestimation of drug exposure. However, the findings confirm the valuable role that fluconazole may have in the treatment of Candida cholangitis and/or peritonitis caused by susceptible strains in LTx patients, and supports the usefulness of TDM for optimizing fluconazole exposure in this setting.

Table 1. Bile and plasma trough levels and bile/plasma ratio of fluconazole in two LTx patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Bile C_{min} (mg/L)</th>
<th>Plasma C_{min} (mg/L)</th>
<th>Bile/plasma ratio</th>
<th>MIC for C. albicans isolate in bile (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.04</td>
<td>17.81</td>
<td>0.51</td>
<td>0.25</td>
</tr>
<tr>
<td>2</td>
<td>6.29</td>
<td>12.61</td>
<td>0.50</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Table 2. Ascites and plasma trough levels and ascites/plasma ratio of fluconazole in one LTx patient

<table>
<thead>
<tr>
<th>Patient</th>
<th>Ascites C_{min} (mg/L)</th>
<th>Plasma C_{min} (mg/L)</th>
<th>Ascites/plasma ratio</th>
<th>MIC for C. albicans isolate in ascites (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>9.60</td>
<td>11.30</td>
<td>0.85</td>
<td>0.25</td>
</tr>
</tbody>
</table>

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Seminal pharmacokinetics and antiviral efficacy of once-daily maraviroc plus lopinavir/ritonavir in HIV-infected patients

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Sir,

Sexual transmission of HIV-1 is currently the major way of viral spread worldwide: the quantification of seminal HIV-1 RNA has been clearly linked to the risk of transmission. The use of highly active antiretroviral treatment, besides providing immunovirological benefits, has been associated with viral control in the genital