C. metapsilosis isolates, regardless of the medium used, were more susceptible to the killing activity of caspofungin. This study is the first comparing caspofungin killing activity against the closely related species C. parapsilosis, C. orthopsilosis and C. metapsilosis. Killing curves, regardless of the medium used, showed a decreasing order of susceptibility to caspofungin: C. metapsilosis > C. orthopsilosis > C. parapsilosis.

Based on high echinocandin MICs for C. parapsilosis sensu stricto, in the case of isolates identified as C. parapsilosis sensu lato low MICs of echinocandins may be regarded as an indicator that an isolate is in fact C. orthopsilosis or C. metapsilosis; in the case of isolates with low echinocandin MICs, DNA-based identification1–3 of the isolates is desirable. Because C. orthopsilosis and C. metapsilosis seem to be relevant species among bloodstream isolates in some countries,2,3 this distinction may be particularly important in some epidemiological situations or in clinical situations when the use of echinocandins as therapy or prophylaxis is planned.

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Transparency declarations

None to declare.

References


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Posaconazole concentrations in the central nervous system

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Sir,

Posaconazole is a new triazole approved for prophylaxis in neutropenic high-risk patients1,2 and as salvage treatment of, for example, invasive aspergillosis.3 Pharmacokinetic analyses suggest an exposure–response relationship.3 Diarrhoea, proton pump inhibitors (PPIs) and elevated gamma-glutamyltransferase are associated with reduced plasma concentrations.3

We report the first three patients in whom posaconazole concentrations in the CNS were determined and related to their respective serum concentrations.

Patient A

A 46-year-old male taking prophylactic posaconazole 200 mg three times a day and prednisone 75 mg intravenously (iv) twice daily for extensive graft-versus-host disease with severe diarrhoea presented with tenderness over the right maxillary sinus accompanied by paresis of cranial nerves III, IV and VI, acute loss of visual acuity of the left eye and a C-reactive protein (CRP) increase to 253 mg/dL. Cranial MRI revealed a space-occupying lesion in the right maxillary sinus and an occluded right internal carotid. The same day, the patient underwent surgery of the maxillary sinuses. Histopathological examination
revealed zygomycosis with vascular invasion. Cladosporium cladosporioides and Rhizopus oryzae were identified by culture and PCR, respectively. The patient died after 2 weeks. During the entire stay, the patient had pantoprazole 40 mg a day orally. For all posaconazole concentrations, refer to Table 1.

**Patient B**

A 26-year-old female patient with hereditary IgG 2/4 deficiency, and recurrent oesophageal candidiasis leading to stenosis, developed two large frontal lobe abscesses under antibacterial treatment for bronchopneumonia. She had been receiving posaconazole 400 mg orally twice daily for 2 years. Drainage revealed Streptococcus mitis. Until deterioration of her neurological status, pantoprazole 40 mg a day orally had been administered. The patient died on the day after drainage.

**Patient C**

A 14-year-old boy with bacterial meningitis, an intracranial pressure probe and bilateral external ventricular drainages (EVDs) revealed imaging signs of bilateral ventriculitis and abscess formation in the left frontal lobe. Aspergillus fumigatus was isolated from a removed EVD and CSF galactomannan index was 3.4. Voriconazole 6 mg/kg twice-daily loading dose and 4 mg/kg twice-daily iv was initiated as well as caspofungin 70 mg a day administering. Until deterioration of her neurological status, pantoprazole 40 mg a day orally had been administered. The patient died on the day after drainage.

### Discussion

We present three patients whose posaconazole concentrations were measured in serum or plasma and CSF or cerebral abscess fluid, respectively. Of note, no tendency towards a fixed plasma/CNS ratio could be observed. Although posaconazole was undetectable in the CSF of Patient A, concentrations in the CNS abscess fluid of Patient B equalled 41% to 47% of his serum levels. The inverse was true for Patient C, whose posaconazole CSF/serum ratio was 2.3 (Table 1). Due to the lack of information on the pharmacokinetic and pharmacodynamic properties of posaconazole in the CNS, we hypothesize on the factors that led to this variation in drug levels.

In Patient A, posaconazole measurements in serum 5 days prior to the onset of symptoms were only 88 µg/L in serum and not measurable in CSF. The low serum levels can be explained by the combination of severe diarrhoea and PPI intake, both factors being associated with decreased intestinal posaconazole resorption. Furthermore, significant cerebral inflammatory activity with a concomitant increase in permeability of the blood–brain barrier cannot be expected at the time point when the sample was taken, accounting for the absence of posaconazole in CSF. Lumbar puncture might have served to corroborate this hypothesis, but was not carried out in this patient.

In contrast, Patients B and C presented with cerebral abscesses and bilateral ventriculitis plus abscess formation, respectively. Under these circumstances, inflammatory disturbance of the blood–brain barrier might have facilitated the penetration of posaconazole into the cerebral abscess fluid in Patient B and into the CSF in Patient C. Although lumbar puncture could not be performed in Patient B, CSF was repetitively analysed in Patient C. On the day of initiation of posaconazole administration, the albumin quotient (CSF albumin/serum albumin × 100) was 4.4, a value that is consistent with a severe disturbance of the blood–brain barrier.

We hypothesize that disturbance of the blood–brain barrier may facilitate passage of posaconazole into the CSF, where it can be quantified by HPLC. Based on these data, posaconazole may be an option in the treatment of cerebral fungal infections, as has been formerly suggested by the promising results from a clinical trial by Pitisuttithum et al.5

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### Transparency declarations

M. K. has been a consultant for Pfizer, Eli Lilly and Roche. G. F. has been a consultant for Schering Plough, Pfizer and Gilead, has served on a speaker’s bureau for Schering.

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### Table 1. Posaconazole measurements in serum and CSF

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sample day (relative to initiation of posaconazole administration)</th>
<th>Sample day (relative to onset of symptoms)</th>
<th>Serum levels (µg/L)</th>
<th>CSF levels (µg/L)</th>
<th>CSF/serum levels (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>14</td>
<td>-5</td>
<td>88</td>
<td>&lt;10</td>
<td>not applicable</td>
</tr>
<tr>
<td>B</td>
<td>&gt;700</td>
<td>1</td>
<td>396</td>
<td>187 (first sample)</td>
<td>47</td>
</tr>
<tr>
<td>C</td>
<td>7</td>
<td>63</td>
<td>not acquired</td>
<td>153 (left EVD)</td>
<td>not applicable</td>
</tr>
</tbody>
</table>

EVD, extraventricular drainage.

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1. Pitisuttithum et al. 2018
2. Fung et al. 2019
3. Gilead, 2018
4. Pitisuttithum et al. 2017

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M. K. has been a consultant for Pfizer, Eli Lilly and Roche. G. F. has been a consultant for Schering Plough, Pfizer and Gilead, has served on a speaker’s bureau for Schering.

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1. Fung et al. 2019
2. Gilead, 2018
3. Pitisuttithum et al. 2017
5. Pitisuttithum et al. 2018

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3. Pitisuttithum et al. 2017
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Autoimmune hepatitis (AIH) results in a chronic inflammatory process in the liver; it is associated with hypergammaglobulinemia and the occurrence of autoantibodies. Diagnosis of AIH often represents a clinical challenge as its clinical presentation is quite heterogeneous. The association of AIH and hepatitis C virus (HCV) infection is well known and when present it generally complicates definitive diagnosis. Difficulties are greater when AIH coexists with both HCV and HIV. Although this is a rare situation, the need for long-term immunosuppressive therapy gives special relevance to this subset of patients.

A young Caucasian woman on regular follow-up at our HIV clinic for more than 15 years initiated treatment for chronic HCV infection in 2006. She had been engaged in intravenous drug addiction practices in her twenties and had acquired an HCV genotype 4 infection. General blood tests (haemoglobin, platelet count and kidney profile) gave normal values. She presented with mild hepatic cytolysis [aspartate aminotransferase (AST) 167 IU/L and alanine aminotransferase (ALT) 189 IU/L], with a normal liver function (albumin 3.25 mg/dL and prothrombin activity 92%). Plasma HCV-RNA was 155 000 IU/mL. Liver fibrosis was measured using transient elastometry (FibroScan®) and was determined to be mild (estimate Metavir F2). She had been on antiretroviral therapy for more than 12 years and currently was receiving tenofovir, emtricitabine and atazanavir/ritonavir as a fourth-line therapy. Plasma HIV-RNA was <50 copies/mL, and CD4 counts were 634 cells/mm³. Her past gynaecological history evidenced two spontaneous abortions. The patient had been vaccinated for hepatitis B virus (HBV) in the past, developing a satisfactory immunological response [hepatitis B surface-antigen antibody (HBsAb) titre 78 IU/mL].

On February 2006, she began treatment with pegylated interferon-α2b (100 µg weekly) plus weight-adjusted ribavirin (1000 mg daily). She did not achieve a rapid virological response, but HCV-RNA was undetectable at week 12 of therapy and until completion of 15 months of treatment. No serious adverse events were reported during therapy. Fifteen days after ending hepatitis C treatment, the patient complained of asthenia, arthralgias, myalgias and low-grade fever. Serum blood biochemistry showed a 10-fold increase in aminotransferases (AST and ALT) and mild non-icteric cholestasis with a normal liver function [international normalized ratio (INR) 1.04 and albumin 3.6 mg/dL]. Serum HCV-RNA remained undetectable (<10 IU/mL). The patient was admitted at the hospital for more thorough evaluation. After ruling out the involvement of hepatotoxic drugs, alcohol consumption, infection with other hepatotropic viruses [hepatitis A virus (HAV), HBV, Epstein–Barr and cytomegalovirus] and metabolic liver disorders (haemochromatosis, Wilson’s disease and α1-antitrypsin deficit), tests for autoimmunity revealed polyclonal immunoglobulin G elevation and anti-nuclear antibodies (ANAs) at titres of 1/20 000. Other types of autoantibodies (anti-smooth muscle antibody, anti-liver and kidney microsome type 1, anti-liver cytosol type 1 and anti-mitochondrial antibody) were all negative, as were plasmatic cryoglobulins. Autoimmune tests had been negative before initiating hepatitis C therapy. During hospital admission, serum HCV-RNA reappeared with low values (800 IU/mL) in May 2007, rose to 48 000 IU/mL in June 2007 and decreased to 18 000 IU/mL in July 2007. HCV genotyping was repeated and no change was found in HCV variant, which could have suggested re-infection. However, spontaneous HCV clearance occurred subsequently and until now 15 months later (Figure 1).