Case report

Cure of chronic invasive sinus aspergillosis with oral saperconazole

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We report a case of chronic invasive aspergillosis of the maxillary sinus which continued to progress despite treatment with high doses of oral itraconazole. The patient was unable to tolerate treatment with intravenous amphotericin B and had limited response to two different lipid-complexed preparations of amphotericin B (AmBisome, Vestar Ltd; Amphocil, Liposome Technology Inc.). Treatment with oral saperconazole (Cilag Ltd) resulted in a dramatic clinical and radiological response but was associated with abnormalities of liver function at a daily dose of 200 mg 12 hourly. These biochemical abnormalities were not associated with clinical symptoms and resolved fully within 2 weeks of reducing the dose to 100 mg 12 hourly. Saperconazole may represent an effective treatment of invasive sinus aspergillosis in patients who are unable to tolerate, or fail treatment with itraconazole and amphotericin B.

Introduction

Aspergillus infection of the sinuses takes one of four forms: acute invasive, chronic invasive, saprophytic (usually as a fungal ball) or allergic [1–3]. A variant of chronic invasive disease is termed paranasal Aspergillus granuloma [2,4,5] because histology shows granulomata intermixed with fungal elements. Antifungal therapy (with itraconazole or amphotericin B) is indicated for the first two forms, usually with surgery. Response rates in non-immunocompromised patients treated medically and surgically are about 75% [4]. We describe a case of chronic invasive Aspergillus infection of the maxillary and ethmoidal sinuses in whom treatment with amphotericin B (Fungizone, AmBisome and Amphocil) and itraconazole (capsules and solution) was unsuccessful but which was eventually successfully treated by the new triazole, saperconazole.

Case history

A previously healthy 34-year-old woman, with no history or findings of any abnormality in immune function, presented in February 1991 complaining of right-sided nasal blockage and discharge with bleeding and watering in her right eye. On examination, her nasal septum was grossly deviated to the right with some crusting around her right nostril. Submucosal resection and biopsy from her right ethmoid sinus revealed large amounts of thickened green necrotic material from which Aspergillus fumigatus was grown. Minimal inhibitory concentrations [5] were 1 µg ml⁻¹ for amphotericin B and itraconazole, and 0.5 µg ml⁻¹ for saperconazole. Histology revealed mucosal oedema with a prominent mixed inflammatory cell infiltrate (lymphocytes, plasma cells, eosinophils and neutrophils) and mucosal invasion by fungal hyphae. No granuloma were seen. CT scan showed an extensive soft tissue mass filling the right nasal cavity and maxillary antrum, extending into the right ethmoid and sphenoid sinuses (Fig. 1). Bony destruction of the nasal septum and medial wall of the right orbit was seen. Despite two extensive internal debridements, the disease progressed and an external ethmoidectomy was performed. Histology again confirmed mucosal infiltration by fungal hyphae (using Grocott stain) and A. fumigatus was cultured from necrotic debris. Full blood count, electrolytes and liver and renal function were normal at presentation.
The patient received itraconazole capsules postoperatively but drug concentrations remained subtherapeutic [6,7] despite doses of up to 800 mg day⁻¹ (Table 1). Higher serum concentrations were achieved with oral administration of itraconazole in cyclodextrine solution (Janssen Pharmaceutica, 200 mg 12 hourly) but this failed to provide clinical or radiological improvement and she required further cavity washouts. Intravenous amphotericin B (at a total dose of 2-65 g over 8 weeks) was given with slight improvement. Because of nausea, treatment was changed to amphotericin B colloidal dispersion (Amphocil, Lipsome Technology Inc.) at a dose of 4 mg kg⁻¹ day⁻¹ (total dose 3-825 g). She showed some improvement but after 3 weeks of treatment partial deafness developed which was attributed to Amphocil. Tests confirmed bilateral sensorineural hearing loss of 40-50 decibels. Treatment was changed (with resulting improvement in hearing) to liposomal amphotericin B (Ambisome, Vestar Ltd) at a daily dose of 100 mg (2 mg kg⁻¹ day⁻¹) for 25 days followed by maintenance with itraconazole solution (400 mg day⁻¹). This was associated with recurrence of her symptoms and serial CT scans confirmed persisting abnormality (including bone destruction) with little change other than the effects of surgical debridement.

In view of treatment failure due to drug intolerance or lack of efficacy, saperconazole (Cilag Ltd) was commenced at an initial dose of 100 mg 12 hourly. Five weeks after starting treatment, the dose was increased to 200 mg 12 hourly; at this time she reported a marked improvement in well-being and dramatic reduction in nasal discharge. After a further 3 weeks, liver function had become abnormal with AST activity rising to 132 IU l⁻¹ (normal <35 IU l⁻¹) and LDH to 861 IU l⁻¹ (normal <40 IU l⁻¹) although alkaline phosphatase, gamma glutamyl transferase, bilirubin and albumin remained normal and she was asymptomatic.

### Table 1 Assays of serum and urine drug concentrations

<table>
<thead>
<tr>
<th>Drug/dose</th>
<th>Formulation</th>
<th>Serum concentration*</th>
<th>HPLC (µg ml⁻¹)</th>
<th>Urine concentration (µg ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Bioassay (µg ml⁻¹)</td>
<td>Itraconazole</td>
<td>Hydroxyitraconazole</td>
</tr>
<tr>
<td>Itraconazole</td>
<td></td>
<td></td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>200 mg 12 hourly</td>
<td>Capsules</td>
<td>0.99 (pre), 1.7 (2.5 h post)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>400 mg 12 hourly</td>
<td>Capsules</td>
<td>1.05</td>
<td>1.7</td>
<td>ND</td>
</tr>
<tr>
<td>100 mg 12 hourly</td>
<td>Solution</td>
<td>0.6</td>
<td>0.8</td>
<td>ND</td>
</tr>
<tr>
<td>200 mg 12 hourly</td>
<td>Solution</td>
<td>6</td>
<td>0.61</td>
<td>1.26</td>
</tr>
<tr>
<td>Saperconazole</td>
<td></td>
<td></td>
<td>6</td>
<td>0.82</td>
</tr>
<tr>
<td>100 mg 12 hourly</td>
<td>Capsules</td>
<td>1.15</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>200 mg 12 hourly</td>
<td>Capsules</td>
<td>1.5</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Steady state unless otherwise specified.

°Measured on different occasions.

†Administered as 10 mg ml⁻¹ of cyclodextrin solution.

HPLC, high performance liquid chromatography; ND, not done.
These abnormalities fully resolved within 2 weeks of reducing the dose of saperconazole back to 100 mg 12 hourly. The patient has now completed 5 months of therapy with saperconazole and a repeat CT scan shows almost complete resolution, leaving only slight mucosal thickening (Fig. 2). She remains well 1 year after discontinuing saperconazole.

Discussion

Chronic invasive fungal sinusitis is a slowly progressive disease seen occasionally in immunocompetent hosts. The distinction between saprophytic and chronic invasive disease rests on histological findings of fungal hyphae infiltrating mucosal tissue and radiological evidence of bony destruction, both of which were present in our patient. A chronic clinical course is characteristic and cure is difficult to achieve even with extensive surgical debridement and appropriate antifungal therapy [3], which need to be given for long periods. The chronicity of antifungal chemotherapy makes intravenous preparations less preferable to an oral agent such as itraconazole. The availability of assays of itraconazole levels enables assessment of compliance and assists in determining an optimal dosage regimen. Itraconazole absorption is usually good but there is considerable inter-patient variability. Higher serum concentrations are required for adequate anti-Aspergillus activity [6]. Nevertheless itraconazole failed to prevent disease progression in our patient. Amphotericin B (Fungizone) was temporarily effective but had to be discontinued because of side-effects. Lipid-complexed preparations of amphotericin B are associated with lower toxicity but also appear to be less effective on a molar basis, requiring higher doses. Ototoxicity has never previously been reported with Amphotec therapy.

Saperconazole is a potent antifungal closely related in structure to itraconazole. It is a selective inhibitor of cytochrome P450-dependent ergosterol synthesis in fungal cells, with a broad spectrum of activity against most fungi, including Malassezia and Sporothrix species [5,8–10]. It is at least as effective as fluconazole against Candida species [8] and has good activity against Aspergillus species both in vitro and in animal models [5,9,10] where it has been reported to have superior activity when compared with itraconazole. This was demonstrated in our patient, who had a good clinical response to treatment. Clinical data on side effects of saperconazole are lacking, as its use has been very limited to date. Abnormalities of liver function have not previously been noted. In our patient, this was clearly dose related and reversible.

The impressive in vitro efficacy of saperconazole against Aspergillus is borne out by our clinical experience. Further clinical studies will more clearly define the place of saperconazole for the treatment of Aspergillus infections, but our experience is encouraging.

References


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