Successful treatment of brain aspergillosis with voriconazole

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ABSTRACT

Until recently, brain aspergillosis was almost always fatal, with a response rate to amphotericin B of <10%. This study describes a retrospective analysis of eight consecutive cases of brain aspergillosis. All patients were immunosuppressed and five required mechanical ventilation. Antifungal treatment included amphotericin B (n = 7), itraconazole (n = 3), voriconazole (n = 2) and flucytosine (n = 1). Three (38%) patients survived following prolonged azole therapy after initial amphotericin B treatment, combined with a reduction in their immunosuppressive treatment. The prognosis of brain aspergillosis might be improved if immunosuppression could be reduced and prolonged oral azole therapy used.

Keywords Aspergillosis, azoles, brain aspergillosis, therapy, voriconazole

Invasive aspergillosis is a major cause of morbidity and mortality in immunosuppressed patients [1–3]. In a cohort study in 1994–1995, complete or partial responses were seen in 132 (40%) of 330 patients with pulmonary invasive aspergillosis, and in 23 (16%) of 148 patients with disseminated aspergillosis [1]. Central nervous system involvement corresponded with the poorest response rate, with complete or partial response reported in three (9%) of 34 patients. A review in 1996 reported a crude mortality rate of 99% (140/141 patients) in cases of brain aspergillosis [4]. However, the development of new azoles active against aspergillosis might improve this situation. To investigate this possibility, eight consecutive patients with brain aspergillosis admitted to the Infectious Diseases intensive care unit (ICU) at Bichat-Claude Bernard Hospital (a 1200-bed university-affiliated teaching hospital that serves as a referral centre in the metropolitan Paris area) were analysed retrospectively.

Brain aspergillosis was defined by the three following criteria: (1) at least one predisposing condition for invasive aspergillosis (bone marrow transplant, haematological malignancy, chronic neutropenia, immunosuppressive treatment); (2) at least one localised lesion visible on computerised tomography brain scan and/or magnetic resonance imaging in the absence of an alternative diagnosis; and (3) isolation of Aspergillus spp. from culture of intracerebral material, bronchoalveolar lavage or sinus samples, or hyphae consistent with the presence of Aspergillus spp. in a biopsy of brain tissue. All patients had definite or probable invasive aspergillosis according to the consensus
guidelines of the European Organisation for Research and Treatment of Cancer (EORTC)/National Institute of Health (NIH)/Mycoses Study Group (MSG) [5]. All patient charts and radiographs were reviewed, and the patients’ sex, age, predisposing factors, symptoms, Glasgow Coma Scale (GCS) score and Simplified Acute Physiology Score (SAPS) II [6,7] were recorded. Surgical and medical treatment and the outcome for each patient at the time of the most recent evaluation, or on the basis of correspondence, were recorded. Identification of Aspergillus spp. was performed with the use of standard microbiological techniques [8].

All eight patients were immunosuppressed (Table 1), and their mean age was 49.5 years (range 46–64 years). Most (6/8) patients developed the first symptoms of brain aspergillosis while hospitalised. Symptoms on first evaluation included fever (n = 6), headache (n = 3), focal neurological manifestations (n = 2) and seizures (n = 1). The chest X-ray was abnormal for six patients, including five patients with lesions suggestive of pulmonary aspergillosis (nodular shadows with and without cavitation). Initial brain computerised tomography scans revealed single (n = 3) or multiple (n = 4) lesions with a median size of 2 cm (range 2–3 cm). Other radiological features included peri-lesional oedema (n = 4), mass effect (n = 3) and brain haemorrhage (n = 1). One patient with a normal brain computerised tomography scan had 15 individual lesions by magnetic resonance imaging. Two patients underwent lumbar puncture; both had elevated protein levels (0.7 and 1.2 g/L), normal glucose levels, and negative results for direct examination and culture of cerebrospinal fluid. One patient had an elevated white cell count (1640/mm³; 95% neutrophils). Aspergillus fumigatus was identified from all seven patients with a positive culture (7/8).

Patients were transferred to the ICU mostly because of neurological deterioration (n = 6). The mean GCS score upon ICU admission was 11.5 (range 7.5–15) and the mean SAPS II score was 34 (21–46). Five (62%) patients died in the ICU, mainly because of neurological deterioration (4/5), including two patients who developed brain stem herniation (one after lumbar puncture was performed). The mean delay between ICU admission and death was 12 days. Three patients survived, with a mean duration of ICU stay of 43 days and a mean follow-up after discontinuation of antifungal treatment of 3 years. These

Table 1. Characteristics of eight consecutive patients admitted to the intensive care unit with brain aspergillosis

<table>
<thead>
<tr>
<th>Sex/Age</th>
<th>Underlying disease</th>
<th>Immunosuppression</th>
<th>Extra-cerebral involvement</th>
<th>Aspergillus spp. isolation</th>
<th>Antifungal treatment</th>
<th>Surgical treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female 61 years</td>
<td>Acute leukaemia</td>
<td>Myeloablative chemotherapy</td>
<td>Lung</td>
<td>BAL.</td>
<td>Ampho B (31 days) Flucytosine (3 days)</td>
<td>None</td>
<td>Died</td>
</tr>
<tr>
<td>Male 67 years</td>
<td>Kidney transplant Chronic myeloid leukaemia</td>
<td>Corticosteroids</td>
<td>Lung</td>
<td>Brain abscess aspiration Brain biopsy (autopsy)</td>
<td>Ampho B (25 days) None*</td>
<td>External diversion None</td>
<td>Died</td>
</tr>
<tr>
<td>Male 32 years</td>
<td>Kidney transplant Chronic myeloid leukaemia</td>
<td>Corticosteroids</td>
<td>None</td>
<td>Brain biopsy</td>
<td>Ampho B (14 days) Ampho B (29 days) Itraconazole (410 days)</td>
<td>None</td>
<td>Died</td>
</tr>
<tr>
<td>Female 43 years</td>
<td>Glioblastoma</td>
<td>Corticosteroids</td>
<td>Lung</td>
<td>BAL</td>
<td>None</td>
<td>None</td>
<td>Cured</td>
</tr>
<tr>
<td>Female 67 years</td>
<td>Wegener granulomatosis</td>
<td>Corticosteroids</td>
<td>Lung</td>
<td>BAL* + brain abscess aspiration</td>
<td>Itraconazole (13 days)</td>
<td>Abscess aspiration</td>
<td>Died</td>
</tr>
<tr>
<td>Male 49 years</td>
<td>Larynx cancer</td>
<td>Myeloablative chemotherapy</td>
<td>Lung</td>
<td>BAL</td>
<td>Ampho B (25 days) Itraconazole (44 days)</td>
<td>Ampho B (380 days)</td>
<td>No</td>
</tr>
<tr>
<td>Female 49 years</td>
<td>Systemic lupus erythematosus End-stage renal disease</td>
<td>Corticosteroids</td>
<td>Lung</td>
<td>BAL</td>
<td>None</td>
<td>None</td>
<td>Cured</td>
</tr>
<tr>
<td>Male 53 years</td>
<td>Wegener granulomatosis</td>
<td>Corticosteroids</td>
<td>Lung, frontal sinus</td>
<td>Frontal sinus aspiration</td>
<td>Ampho B (28 days) Voriconazole (460 days)</td>
<td>No</td>
<td>Cured</td>
</tr>
</tbody>
</table>

Ampho B, amphotericin B; BAL, bronchoalveolar lavage.

*The diagnosis of brain aspergillosis was post-mortem.

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three patients received intravenous treatment with deoxycholate amphotericin B, followed by liposomal amphotericin B (mean duration of 33 days), followed by prolonged oral azole treatment (mean duration of 14 months). For these patients, immunosuppression could be reduced by a dose reduction in their corticosteroid treatment. Two of these patients had no neurological sequelae at the time of last evaluation.

Although amphotericin B has been the mainstay of treatment for invasive aspergillosis since 1959 [3,9], the superiority of voriconazole over amphotericin B as initial therapy for invasive aspergillosis in terms of response rate, survival rate and safety has now been demonstrated [10]. Brain aspergillosis has a crude mortality rate estimated to be between 90% and 99% in the largest studies [1,4,11], and it may be this localisation that will benefit most from the development of new azoles. Voriconazole could be the preferred treatment for this indication, as it can be given orally and has a good safety profile [12]. The superiority of voriconazole over amphotericin B for the initial treatment of invasive aspergillosis has been demonstrated in a large randomised study [10], whereas a separate study failed to show any significant advantage for itraconazole [13]. Voriconazole also has a favourable pharmacokinetic profile, with good blood–brain barrier penetration and a mean cerebrospinal fluid concentration/plasma concentration ratio ranging from 0.22 to 1.0 [14,15], so that voriconazole levels were above the minimal fungicidal concentration for Aspergillus spp. in most cerebrospinal fluid specimens tested in one study [16]. Among the other drugs currently licensed for the treatment of invasive aspergillosis, amphotericin B and its lipid formulations, as well as itraconazole and caspofungin, are unable to achieve consistently measurable concentrations in cerebrospinal fluid. More clinical studies are needed for other new azoles such as ravuconazole or posaconazole.

The present study describes eight patients with severe invasive aspergillosis, similar to those described in previous series [3,11,17,18]. In addition to the brain localisation of their aspergillosis, these patients were admitted to the ICU, which has been associated with a mortality rate of 92% [19,20]. In the present study, three patients had no signs of aspergillosis relapse at 3 years following the discontinuation of antifungal treatment. This favourable outcome could be associated with their potentially reversible immunosuppression and their prolonged treatment with suppressive antifungals. Thus, the prognosis for brain aspergillosis might be improved if immunosuppression could be reduced and prolonged oral azole therapy used.

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RESEARCH NOTE

Morphological changes induced by imipenem and meropenem at sub-inhibitory concentrations in Acinetobacter baumannii

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ABSTRACT

Sub-inhibitory concentrations of imipenem and meropenem were evaluated for their ability to induce morphological changes with six strains of Acinetobacter baumannii isolated from patients with nosocomial pneumonia. Three strains were susceptible and three were resistant to carbapenems. The strains were grown in the presence of 0 (controls), 0.25×, 0.5× and 1× the MIC of both carbapenems for 4 h, and then examined after Gram’s stain. Cells ≥3 µm in size (spheroplasts) were considered to be altered. Both carbapenems induced significant numbers of spheroplasts compared to controls. Imipenem had more effect against susceptible strains, while meropenem had a greater effect against resistant strains.

Keywords Acinetobacter baumannii, carbapenems, imipenem, meropenem, sub-MIC activity, ultrastructural changes

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Various antimicrobial agents are known to retain some activity at sub-MIC concentrations, causing bacteria to undergo ultrastructural changes [1–3]. These changes promote opsonisation and phagocytosis [4–6], resulting in bacterial clearance by the immune system, and explain, at least in part, pharmacodynamic phenomena such as the post-antibiotic effect [7]. Penicillins and cephalosporins induce the formation of filamentous forms because their primary target is penicillin-binding protein 3 (PBP3) [1–3]. Several studies with carbapenems have revealed the formation of round cells (spheroplasts) with different species of Gram-negative bacteria [8–11]. This differential pattern has been explained by the affinity of carbapenems for PBP2.

In the clinical setting, there are periods between doses when the concentrations of antimicrobial agents fall below the MICs for the infecting bacteria; nevertheless most β-lactams will achieve a bacteriological cure in many clinical scenarios, provided that the concentration remains above the MIC for ≥40% of the interval between doses; indeed, this period may be even shorter (25–30%) with carbapenems because of their prolonged post-antibiotic effect [12]. Hence, the sub-MIC activity (SMA) plays a significant role in antimicrobial therapy. This role may be of particular relevance with multiresistant pathogens such as Acinetobacter baumannii, which is now considered to be one of the most important nosocomial bacteria [13]. However, to our knowledge, there are no data on the SMA of carbapenems against A. baumannii. Therefore, the aim of the present study was to assess the in-vitro SMA of imipenem and meropenem against six clinical isolates of