Treatment of Cerebral Aspergillosis with Itraconazole: Do High Doses Improve the Prognosis?

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We describe a 72-year-old woman with chronic asthma who presented with cerebral abscesses due to Aspergillus fumigatus after she received treatment with corticosteroids. Therapy with high-dose itraconazole (800 mg/d for 5 months, followed by 400 mg/d for an additional 4.5 months) resulted in complete resolution of all lesions. Serum concentrations of the drug ranged from 2 μg/mL to 30 μg/mL. Review of 20 cases of cerebral aspergillosis that were treated with itraconazole revealed that three of the four patients who received high doses (800 mg/d in the adults) of the drug responded favorably, while only two of the 16 patients who received a dose of 400 mg/d were cured. The use of high-dose itraconazole appears to be justified for high-risk patients with cerebral aspergillosis for whom conventional therapy has failed.

Cerebral aspergillosis has a poor prognosis. We describe a case of multiple cerebral abscesses caused by Aspergillus fumigatus that was cured with high doses of itraconazole, and we review the literature that describes the drug’s use for this indication.

Case Report

A 72-year-old female with a history of asthma was admitted to another hospital on 21 January 1993 for treatment of an asthmatic episode and required high doses of corticosteroids to control her symptoms. Within a few days she developed progressive right hemiparesis and partial motor seizures in her right arm. A cranial CT scan revealed three hypodense lesions (figure 1); the paranasal sinuses appeared normal. On physical examination, she was stuporous, with right hemiplegia and a slight left hemiparesis; there were no signs of cranial nerve abnormalities, and she was afibrile. ELISA for antibodies to HIV was negative. Stereotaxic puncture of two cerebral lesions yielded 5 mL of pus, and culture of the pus yielded Aspergillus fumigatus. Treatment was begun with amphotericin B (0.65 mg/[kg \cdot d]), with no noticeable clinical improvement.

On day 15 of treatment, a repeated cranial CT scan revealed new lesions (figure 2), which led to the discontinuation of amphotericin B therapy on 5 March 1993 and the initiation of oral itraconazole therapy at a dosage of 400 mg every 12 hours after meals. MICs determined with use of a plate microdilution method similar to that described by Schmitt et al. [1] were 4.0 μg/mL for amphotericin B and 1.0 μg/mL for itraconazole.

Clinical improvement in her condition was noted 1 week later, followed by a slow, progressive recovery. The patient tolerated itraconazole well, although hypokalemia and edema developed.

At discharge in May 1993, she needed assistance with walking because of a discrete residual right hemiparesis that finally resolved in August 1993. On 19 August 1993 the dosage of itraconazole was adjusted (table 1), and in November 1993 a

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Figure 1. Initial cranial CT scan (with contrast) of a patient with cerebral aspergillosis, showing two of three hypodense ring-enhancing lesions localized in both frontal lobes and surrounded by edema.
cranial CT scan revealed only residual lesions (figure 3). In December 1993, administration of itraconazole was stopped. One year later the patient remained asymptomatic, and findings on cranial CT had not changed.

Discussion

The treatment of cerebral aspergillosis has been discouraging. In a review by Denning and Stevens [2], only eight of 33 patients responded to treatment; the mortality rate was nearly 60%. Similarly, in a study by Kim et al. [3] there were only five survivors among 36 immunologically competent subjects with cerebral aspergillosis.

Itraconazole has good in vitro and in vivo activity against *Aspergillus* species [4], and some clinical trials indicate that its efficacy is at least similar to that of amphotericin B in patients with invasive aspergillosis [5]. On the basis of the limited experience available so far, itraconazole appears to be useful in the treatment of cerebral aspergillosis. Table 2 provides a summary of the 12 published cases in which individual details were available. Doses of itraconazole have varied from 400 mg/d to 800 mg/d, and the duration of treatment (which could not be determined in five cases) varied from 0.3 months to 12 months. Eight of the 12 patients described in table 2 died. The other four patients were reported to be cured, and two of these (cases 1 and 12) were followed up after treatment for 6 months and 12 months, respectively. It is noteworthy that three of the four patients treated with high doses of itraconazole survived, while seven of the eight patients treated with the conventional dose of 400 mg/d died.

In addition, in a recent study [12] of the responses of 76 patients with invasive aspergillosis who were treated with itraconazole,

**Table 1.** Dosages and serum concentrations of itraconazole in a patient with cerebral aspergillosis.

<table>
<thead>
<tr>
<th>Date</th>
<th>Dosage (mg/d)*</th>
<th>Serum concentration (μg/mL)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/5/93</td>
<td>800</td>
<td>ND</td>
</tr>
<tr>
<td>3/24/93</td>
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<td>2.00</td>
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<tr>
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<td>800</td>
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<tr>
<td>8/19/93</td>
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</tr>
<tr>
<td>10/21/93</td>
<td>400</td>
<td>12.22</td>
</tr>
</tbody>
</table>

NOTE. ND = not done.
* Administered every 12 hours.
† Determined by bioassay.

**Figure 2.** On day 15 of treatment with amphotericin B, a second cranial CT scan reveals new lesions in both occipital regions.

**Figure 3.** After 8 months of treatment, a cranial CT scan shows only a small hypodense area in the left frontal lobe that did not show enhancement with contrast medium; another similar lesion in the left semioval center is not shown.
seven treatment failures occurred among eight patients with CNS involvement; these patients received 600 mg/d for 4 days, followed by 400 mg/d. Clinical response was associated with detectable serum concentrations of the drug, while treatment failure was associated with the inability to detect the drug in serum.

In summary, our review revealed that three of four patients who received high doses of itraconazole responded favorably, while only two of the 16 patients who received the drug at a dose of 400 mg/d were cured (\( P = .03 \), two-tailed Fisher’s exact test).

Thus, our case and the limited experience reported in the literature suggest that itraconazole may have a role in the treatment of cerebral aspergillosis if used at high doses (800 mg/d in adults); however, strict observance for possible side effects—especially hypokalemia—is necessary, and monitoring of serum concentrations of the drug is recommended.

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### References