Successful Treatment of Multiple Cerebral Histoplasmosas with Itraconazole

Amphotericin B has been suggested as the treatment of choice for cerebral histoplasmosas, but it is effective in only about half of cases [1]. In the review by Wheat et al. [1], no cases of cerebral histoplasmosas resolved without antifungal therapy, and only two were treated with azoles. I am unaware of previous reports of itraconazole use for CNS histoplasmosis.

A 53-year-old woman with a history of type II diabetes mellitus presented with a 3-week history of confusion, dysarthria, right-sided weakness, left-sided eyelid ptosis, weakness of gaze to the right, right-sided hyperreflexia, and left-sided neglect. She denied having chills or sweats and was afebrile.

Four months earlier, she had had a platelet count of 5,000/mm³ and was treated with corticosteroids and intravenous immunoglobulin for idiopathic immune thrombocytopenia. During that time, she had a brief febrile illness; a bone marrow examination revealed noncaseating granulomas, and a chest radiograph showed increased interstitial markings. Her platelet count, fever, and chest radiograph returned to normal after a few days, and corticosteroid treatment was tapered and then discontinued 3 weeks before her neurological symptoms began.

At the time of her neurological symptoms, an MRI scan revealed numerous lesions (diameter, <1 cm) of the grey and white matter of the frontal, parietal, and occipital lobes and lesions within the midbrain and brain stem (figure 1). The lesions enhanced after intravenous injection of gadolinium, and some had surrounding edema. An abdominal CT scan showed the left adrenal to be 3.4 × 3.9 cm with a hypodense center and hyperdense rim. A chest radiograph was normal. A fine-needle adrenal aspirate showed nondiagnostic results. On CSF testing, the following values were noted: glucose, 52 mg/dL; protein, 61 mg/dL; RBCs, 0/mm³; WBCs, 1/mm³ (100% mononuclear). Bone marrow and CSF cultures were negative. The Histoplasma capsulatum polysaccharide antigen level in serum was 0.5 U and in CSF was 0.7 U. The patient was negative for IgG antibodies to Echinococcus species and HIV and IgM antibodies to Toxoplasma species in serum. Her serum was positive for IgG antibodies to Toxoplasma species, but the ratio of Toxoplasma IgG antibodies to total IgG was twofold greater in serum than in CSF. Her titer of complement fixation antibody to H. capsulatum in CSF was 1:2 for the mycelial antigen and 1:4 for the yeast antigen. An open adrenal biopsy revealed extensive necrosis, granulomatous inflammation, and organisms consistent with histoplasmosis. Culture of adrenal tissue yielded H. capsulatum.

The patient refused therapy with amphotericin B. She began receiving itraconazole, 200 mg three times daily for 3 days, followed by 200 mg twice daily. Her neurological signs and symptoms improved over the next 3 months, and repeat MRI scans revealed a decrease in the number and size of the lesions and in the surrounding edema. She continued to receive itraconazole for 1 year. Another MRI scan done 4 months after discontinuation of therapy revealed no change from the scan at the end of therapy. More than 2.5 years after discontinuing therapy, the patient remains asymptomatic.

The patient described had evidence of cerebral histoplasmosas, despite the lack of a brain biopsy. H. capsulatum was found in the adrenal gland, antibodies to H. capsulatum were present in CSF, and the lesions and symptoms responded to antifungal therapy. Negative cultures of CSF and a negative result on CSF histoplasma polysaccharide antigen testing are observed in about half of cases of CNS histoplasmosis [1]. It is likely that her disease was related to the immunosuppressive effects of the corticosteroids, despite discontinuation of corticosteroids 3 weeks before her neurological symptoms began.

Two cases of cerebral histoplasmosas have been successfully treated with ketoconazole after relapse following therapy with intravenous amphotericin B [2, 3]. There has also been a report of treatment failure with ketoconazole therapy for cerebral histoplasmosas [4]. Ketoconazole has been associated with treatment failures in immunocompromised patients with histoplasmosis and has poor penetration into CSF [1]. Two reported cases of CNS histoplasmosis have been treated with fluconazole, which crosses the blood-brain barrier, but the length of follow-up was short [5, 6]. Fluconazole is associated with treatment failures and relapses in both immunocompetent and immunocompromised patients with histoplasmosis and is less active than itraconazole against H. capsulatum in vitro [7].

Itraconazole is more active than ketoconazole or fluconazole in non-CNS histoplasmosis [7, 8]. In animal models, concentrations of itraconazole in CSF are negligible, but concentrations in brain...
tissue exceed those in plasma, which may explain itraconazole’s utility in cases of cryptococcal and coccidioidal meningitis and cerebral aspergillosis [8–10]. Itraconazole use should be considered for cerebral histoplasmosomas, especially in patients who cannot tolerate treatment with amphotericin B or who have amphotericin B treatment failure.

David M. Bamberger
University of Missouri–Kansas City School of Medicine, Kansas City, Missouri

References

Successful Treatment of Ventriculitis Due to Carbapenem-Resistant Acinetobacter baumannii with Intraventricular Colistin Sulfomethate Sodium

Over the past 2 decades, Acinetobacter baumannii has developed one of the most alarming patterns of antibiotic resistance ever observed [1]. Nowadays, since an increasing proportion of isolates are resistant to all antibiotics tested routinely, therapy is a serious challenge [2]. Beginning in 1992, a large outbreak due to multiresistant A. baumannii was noted in our 1,000-bed tertiary teaching hospital, causing considerable imipenem overuse [3]. In January 1997, two clones resistant to carbapenems emerged: clone D, moderately resistant to imipenem (MICs, 4–16 mg/L) and tobramycin (MIC, 8 mg/L) and susceptible only to sulbactam and polymyxins (MICs, ≤4 mg/L), and clone E, highly resistant to imipenem and sulbactam (MICs, >256 mg/L), moderately resistant to tobramycin (MIC, 8 mg/L), and susceptible only to polymyxins. Since then, five patients have developed catheter-associated ventriculitis due to carbapenem-resistant A. baumannii strains (table 1). Of these five patients, three died of their infection after receiving inadequate therapy (patients 1–3). The other two are, to our knowledge, the first reported to date who survived after treatment with intraventricular colistin sulfomethate sodium (patients 4 and 5).

Patient 4 was a 16-year-old boy who underwent surgery and the insertion of an external ventriculostomy tube for continuous drainage because of hemangioblastoma of the fourth ventricle. On day 7 after surgery, meropenem at 2 g/8 h was started empirically to treat his fever, although CSF cultures had been sterile. On day 16, his fever increased, and CSF analysis revealed 27,900 cells/mm³ (95% polymorphonuclear cells), and cultures of CSF yielded A. baumannii. Meropenem was discontinued, and intraventricular tobramycin (10 mg/12 h), intravenous tobramycin (5 mg/kg once a day), and intravenous sulbactam (2 g/6 h) were then initiated. On day 19, because CSF cultures remained positive, the ventriculostomy tube was replaced and intraventricular tobramycin was switched to intraventricular colistin sulfomethate sodium (5 mg/12 h), intravenous tobramycin was maintained, and intravenous sulbactam was discontinued. Intraventricular colistin was administered in a 5-mL solution of saline serum through the ventriculostomy tube after previous extraction of 5 mL of CSF, and thereafter, the drainage was interrupted for 3 hours. On day 21, cultures of CSF were negative and remained so until colistin sulfomethate sodium therapy was ended on day 39, when a ventriculoperitoneal shunt was inserted. During therapy, CSF bacterial titers at 3 hours after colistin sulfomethate sodium administration (peak) were 1/2, and before doses were administered (trough), titers ranged from <1/2 to 1/4. Similarly, CSF bacteriostatic titers at peak were 1/8 and at trough ranged from 1/4 to 1/16. Levels of tobramycin in CSF varied from 7.9 mg/L (peak) to 0.7 mg/L (trough). No adverse reactions were documented during therapy. On day 82, the patient was alert with spontaneous mobilization of the extremities, but he died suddenly of cardiac arrest. Postmortem examination ruled out ventriculitis, and cultures of CSF were negative for A. baumannii.

Patient 5 was a 34-year-old woman who required an external ventriculostomy tube because of subarachnoid hemorrhage with hydrocephalus. The catheter was removed 6 days after insertion; however, 24 hours later, the patient developed high fever and neurological symptoms worsened, with purulent secretion from the catheter insertion site. CSF obtained through a new ventricular drainage site was cloudy, showing 2,000 cells/mm³ (95% polymorphonuclear cells) and short gram-negative rods on gram stain. Cultures from the purulent secretion and CSF yielded A. baumannii. Intraventricular colistimethate sodium (5 mg/12 h), given following the above-mentioned procedures, and intravenous tobramycin (4 mg/kg once a day) were administered without complications. Although a rapid decrease in the bacterial count in CSF...