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PHARMACOLOGY

Isavuconazole Diffusion in Infected Human Brain

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ABSTRACT We report the cases of a 39-year-old woman with chronic lymphocytic leukemia and a 21-year-old man with chronic granulomatous disease treated for cerebral aspergillosis. The patients required radical surgery for infection progression despite adequate isavuconazole plasma concentration or neurological complication. We thus decided to measure the brain isavuconazole concentration. These results suggest that the concentrations of isavuconazole obtained in the infected brain tissue clearly differ from those obtained in the normal brain tissue and the cerebrospinal fluid.

KEYWORDS cerebral aspergillosis, isavuconazole, pharmacokinetic, therapeutic drug monitoring

First, we report the case of a 39-year-old persistently neutropenic woman with chronic lymphocytic leukemia (CLL) admitted to hospital because of headache and fever. Magnetic resonance imaging (MRI) showed several cerebral abscesses. A cerebral biopsy was performed and showed acute septate thin hyaline filamentous fungi. Fungal culture grew *Aspergillus fumigatus* susceptible to triazoles with MICs at 0.5 mg/liter for voriconazole (VCZ), at 0.19 mg/liter for posaconazole, and at 0.38 mg/liter for itraconazole. She initially received 2 weeks of liposomal amphotericin B (L-AmB) in combination with VCZ followed by VCZ monotherapy. Three months after the diagnosis of aspergillosis, she received bendamustin for CLL progression, leading to a more profound neutropenia for 2 weeks. She experienced clinical deterioration with seizures associated with MRI worsening and low VCZ plasma residual concentration (0.790 mg/liter). At that time, we added a treatment with high-dose caspofungin (150 mg/day). She improved clinically, but 2 months later she developed severe cytolytic hepatitis ascribed to voriconazole, which was switched for isavuconazole (ISZ), 200 mg/day after the loading dose. ISZ plasma residual concentrations were 2.5 mg/liter, and 1 month thereafter, the patient reported frontal headache again. A new MRI showed a large edema surrounding the frontal lesions, radical surgery was performed, and the ISZ dosage was increased to 300 mg daily to reach higher plasma residual concentrations (4.3 mg/liter). Fungal culture remained positive. Four months after surgery, while she was still on ISZ and caspofungin, the frontal lesion increased again, and she underwent another neurosurgical intervention, and this opportunity was taken to measure ISZ local concentrations (Fig. 1). In the same period, the ISZ concentration in cerebrospinal fluid (CSF) was undetectable. Fungal culture remained positive. Plasma and tissue ISZ concentrations were measured using a method previously published by our group (1). Tissue samples

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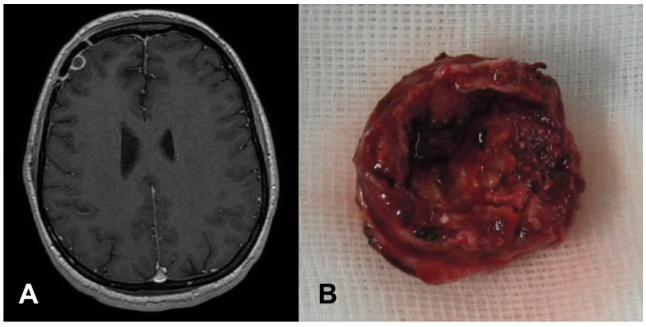

FIG 1 (A) T1-gadolinium cerebral magnetic resonance imaging showing a frontal abscess due to *Aspergillus fumigatus* infection before the second surgical procedure and (B) the resection specimen.

were first diluted 1/5 with water and homogenized as previously described (2), considering a tissue density of 1.04 (3). The following results were obtained: 0.405 mg/liter in normal brain, 2.62 mg/liter in inflamed dura mater, and 5.11 mg/liter and 5.09 mg/liter within the fungal abscess from the first and second surgical procedures, respectively. The corresponding plasma concentrations were 4.3 mg/liter and 3.2 mg/liter, respectively, with a 300 mg daily ISZ dosage. We also verified that the most recent *Aspergillus fumigatus* isolate obtained remained susceptible, with MICs at 1 mg/liter for VCZ and ISZ (EUCAST methodology).

More recently, we managed the case of a 21-year-old man with chronic granulomatous disease treated for probable pulmonary aspergillosis and cerebral aspergillosis since 2013. The diagnosis relied on microscopic morphological findings compatible with *Aspergillus*. In addition to two initial radical surgeries, two interventions were necessary for excision of cystic lesions responsible for brainstem compression and blocking of CSF flow. The patient received different antifungal treatments (VCZ and caspofungin, then posaconazole, then VCZ and caspofungin, then liposomal amphotericin B, then VCZ, then VCZ and caspofungin) and interferon gamma immunotherapy. Finally, an allogeneic bone marrow transplant procedure was performed 2 years after the aspergillosis diagnosis because of refractory infection. The VCZ treatment had to be changed to ISZ (oral treatment, 200 mg/day once daily after the loading dose) due to phototoxicity. One and then two years thereafter, two neurosurgical procedures were needed to remove cystic cerebellar lesions. We proved mycological failure during the first one with a positive culture with *Aspergillus fumigatus* sensitive to all azoles. Thus, measurement of the ISZ concentration in the central nervous system was performed during the last surgical intervention. The concentration in the noninfected cerebellar tissue was below the limit of detection (i.e., 0.025 mg/liter) and was 0. 7949 mg/liter in the cystic wall. Pathological examination of the cystic wall showed a gliotic and fibro-inflammatory tissue, while microbiological tools, including a molecular approach, failed to reveal aspergillosis locally. At the same time, the ISZ plasma concentration was 5.606 mg/liter.

Until now, there were scarce data available on ISZ diffusion in human brain (4). In our first case, we found a high ISZ concentration (more than 5 mg/liter) in the brain abscess, even higher than those expected in plasma (i.e., 2 to 5 mg/liter) (5). We also found encouraging ISZ concentrations in inflamed meninges, contrasting with much lower concentrations in normal brain. With the second case, we confirmed that the concentrations of isavuconazole obtained in the brain markedly differed between inflammatory and normal tissues. Of note, although evidenced in only the two patients studied, our data suggest that the daily isavuconazole dosage might be increased to 300 mg/day during cerebral aspergillosis.

Our pharmacokinetic data obtained in a patient with cerebral aspergillosis are reminiscent of those obtained preclinically and are concordant with an animal model (6) and the efficacy of ISZ in experimental cryptococcal meningitis (7), cerebral mucormycosis (8), or endophthalmitis caused by *Aspergillus fumigatus* (9). In humans, data

regarding the efficacy of ISZ during cerebral fungal infections are scarce (4, 10), considering that results of the noninferiority SECURE trial comparing ISZ to VCZ for the treatment of invasive aspergillosis or those of the VITAL trial involving patients with mucormycosis did not report specifically the efficacy of ISZ in those with cerebral mold infections (11, 12). Even if the examination of the relationship between brain antifungal pharmacokinetics and efficacy were limited, we can note that a high isavuconazole concentration in infected tissue is obtained.

Alternative hypotheses for treatment failure might have been the patient's sustained immunosuppression, as the efficacy of isavuconazole is reduced during neutropenia (13) more than ISZ, based on the MIC values obtained here, as only those >16 μg/ml were associated with reduced efficacy (14).

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