Amphotericin B as Alternative to Itraconazole in Secondary Prophylaxis of Neurohistoplasmosis in HIV-Positive Patients with Antiretroviral Therapy

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Histoplasmosis is a dimorphic pathogenic fungus which causes human infection worldwide, mainly in ecuatorial countries [1]. In immunocompetent patients the most common clinical manifestations consist in a lack of symptoms or a self-limited flu-like profile. However, disseminated histoplasmosis, which represents the 0.05% of the acute infections, is observed in immunosuppressed patients (most of them HIV infected or treated with immunosuppressive drugs), and the illness manifestations are indistinguishable from tuberculosis. Central nervous system (CNS) involvement is exceptional and affects 5-10% of patients with disseminated illness and only 26 previous cases of meningitis caused by this microorganism were described in the last decade [2]. The majority of these patients are treated with nonnucleoside reverse-transcriptase inhibitors, and it is necessary to notice that interaction between these drugs and itraconazole (used in the prophylaxis of these infections) exists. Although this drug-drug interaction is really presumed, the international literature review using MEDLINE database and EMBASE (keywords: interaction ± itraconazole ± nonnucleoside ± reverse-transcriptase ± inhibitors) showed only 3 previous cases [3-5]. It is interesting to report here, because of its rarity, one case of acute meningitis due to Histoplasma, whose treatment and prophylaxis failed initially because of drug-drug interaction between itraconazole and nonnucleoside reverse-transcriptase inhibitors.

A 32-year-old Bolivian man, who lived in Spain for the last three years, with a medical history in his youth of Guillain-Barré syndrome, a doubtful pulmonary tuberculosis, malaria, without sequels, and a recent HIV infection classified as CDC stage C3, whose initial manifestation six months before was a septic shock caused by a disseminated infection due to a filamentous dimorphic fungus identified as Histoplasma (the microorganism grew in bronchial aspirated, blood and bone marrow samples), was admitted into our hospital because of headache, vomiting, walking instability and disrupted speech. He received prophylactic itraconazole oral solution, 200 mg twice a day, and highly-active antiretroviral therapy (HAART) with tenofovir/emtricitabine/efavirenz, ethambutol was initiated. Two weeks later the patient was discharged into the hospital because of his condition worsened. This time, a long term treatment with liposomal amphotericin B for 16 weeks was decided (5 mg/Kg/d). HAART was changed to emtricitabine/tenofovir disoproxil fumarate plus lopinavir/ritonavir because of discordant response and suspected drug-drug interaction between itraconazole and efavirenz. Excellent clinical and analytic improvements were observed and weekly secondary prophylaxis with liposomal amphotericin B was kept (5 mg/Kg) for a year, because of the impossibility of checking itraconazole levels in our laboratory. For that reason we did not obtain urine histoplasma antigen either for monitoring therapeutic effectiveness, as guides recommend [6]. Lumbar puncture at the end of the treatment and after one year with prophylaxis with amphotericin B were normal. After a 2-year follow-up without prophylaxis, the patient is asymptomatic with a CD4 cell count around 350/ml.

The diagnosis of neurohistoplasmosis is difficult, and it is established through the clinical evidence of NCS involvement and one of these: a) CSF antibodies; b) CSF antigen; c) culture isolation in CSF or histologic demonstration in the brain or meningal tissues. However, the diagnosis of chronic isolated CNS infection can be complex, because the serological tests, the direct observation and the CSF cultures are usually negative [2]. The better therapy for neurohistoplasmosis is unknown [2]. The few suggested guidelines are based on some outcomes CNS histoplasmosis described in the literature and in our own experience [1-2]. Treatment

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must be prolonged, and the most optimal is liposomal amphotericin B at 5 mg/Kg/day for 6-16 weeks. Therapy could continue with itraconazole (200 mg 2-3 times/day), until at least one year of treatment is completed. Our case is an example of secondary prophylaxis with liposomal amphotericin B as an alternative to itraconazole, which could be useful if it is not possible to check itraconazole levels or to obtain urine histoplasma antigen [7]. In case of severe immunodeficiency lifelong treatment could be necessary. On the other hand, patients with a good immune response (CD4 cell count higher than 150 cells/mm3) could stop the therapy [8].

However, it is necessary to remember that itraconazole is mainly metabolized to hydroxyitraconazole by the cytochrome P450 34A enzyme [9]. This enzyme takes part in the nonnucleoside reverse-transcriptase inhibitors. It is also necessary to remember that ritonavir is a CYP3A4 inhibitor. Therefore, if protease inhibitors are used, itraconazole levels could be increased, and it is necessary to check itraconazole levels. Some works have demonstrated that when we administer efavirenz and itraconazole together, the bioavailability of itraconazole is lower [3,9]. Consequently we should remember that prophylaxis of neurohistoplasmosis can fail because of drug-drug interaction between itraconazole and nonnucleoside reverse-transcriptase inhibitors and ritonavir. If it is not possible to check itraconazole levels, prophylaxis with amphotericin B is useful.

References