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Case Report Open Access

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

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Histoplasma is a dimorphic pathogenic fungus wich causes human infection worldwide, mainly in ecuatorial countries [1]. In immunocompetent patients the most commun clinical manifestations consist in a lack of symptoms or a self-limited flu-like profile. However, disseminated histoplasmosis, wich 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 this 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 rareness, 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, with a good virological response and a CD4 cell count around 200. The physical examination revealed a temperature of 38.0ºC, neck stiffness, dysarthria and ataxia. Lumbar puncture showed a clear cerebrospinal fluid (CSF) with a white blood cell count of 110/µl (90% mononuclear), proteins 384 mg/dl, glucose 24 mg/dl and adenosine deaminase (ADA) 18 U/l. Cultures, bacilloscopies, India ink staining and serology for *Treponema sp.* in CSF were negative. Simple radiologic study of thorax showed fibrotic lesions in both upper pulmonary lobes and residual granulomas. The brain scanner only evidenced cortico-subcortical atrophy. Sputum and blood cultures were finally negative. Meningoencephalitis by *mycobacteria* was suspected and a treatment with isoniazid, rifampicin, pyrazinamide and ethambutol was initiated. Two weeks later the patient was discharged because of CSF and clinical recovery.

However, two moths later, the patient was admitted again with a similar clinical profile, while the newly obtained CSF showed 100 cells (90% mononuclears), glucose 35 mg/dl, proteins 310 mg/dl and ADA 14 U/l. Bacilloscopies, Löwenstein-Jensen Culture, PCR for mycobacteria, India ink staining and serology were negative again. Brain scanner and magnetic resonance (with/without gadolinium) were normal. Because of the case severity and the evidence of the previous treatment's failure, we decided to initiate a long term therapy with liposomal amphotericin B (4 mg/Kg/d) for four weeks, followed by secondary prophilaxis with itraconazole (200 mg twice a day). Subsequent serology tests in CSF for *Treponema, Brucella, Borrelia*, CMV, EBV, SHV 1 and 2, herpes virus group 6, 7, and 8, *Toxoplasma*, enterovirus and JC-virus, were negative. Serology tests in blood samples for *Tenia solium* (IgG), *Blastomices* (IgG), *Coccidiodes* and *Paracoccidiodes* were negative. Antibodies against *Hystoplasma capsulatum* (IgG) were positive. Plasma PCR for *Hystoplasma capsulatum* was positive. All these tests were done in the Carlos III National Health Institute, Madrid.

Despite this, two months later the patient had to be readmitted into 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 impossiblility 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 stablished through the clinical evidence of NCS involvement and one of these: a) CSF antibodies; b) CSF antigen; c) culture isolation in CSF or hystologic 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 prohylaxis with liposomal amphotericin B as an alternative to itraconazole, wich could be useful if it is not possible to check itraconazole levels or to obtain urine histoplasma antigen [7]. In case of severe immunodeficiency life-long 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, itraonazole levels could be increased, and to check itraconazole levels is recommended. 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.

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