Case Report

High-dose benznidazole in a 62-year-old Bolivian kidney transplant recipient with Chagas central nervous system involvement


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**ABSTRACT**

There is little published data on benznidazole dosing, or levels in cerebrospinal fluid. In this report, we describe the clinical course of an immunosuppressed patient with Chagas central nervous system involvement. He was treated successfully with larger benznidazole doses than are recommended, in order to reach therapeutically effective concentrations in the brain.

**Introduction**

Currently, only two effective drugs are available for the treatment of Chagas disease: benznidazole and nifurtimox (World Health Organization, 2018; Pérez-Molina and Molina, 2017). Information on the pharmacokinetics of benznidazole is limited (Molina et al., 2017). Here, we present the case of a kidney transplant recipient with Chagas disease and central nervous system (CNS) involvement, whose poor clinical course required treatment with much higher doses of benznidazole than are recommended.

**Case report**

A 62-year-old man from Bolivia was admitted to hospital because of focal neurological deficits. The patient, who had been living in Spain for more than 10 years, had a medical history of chronic kidney disease on haemodialysis treatment starting in 2012. He underwent a kidney transplantation from a deceased donor in 2014, and was receiving long-term immunosuppression with prednisone 5 mg/24 h, tacrolimus at a dose to achieve trough levels of 6–8 ng/ml, and mycophenolic acid at 360 mg twice daily. In July 2016, he showed an increase in proteinuria and his graft was biopsied. The findings were consistent with chronic active antibody-mediated rejection, without HLA donor-specific antibodies. Therefore, steroid pulses at 10 mg/kg/day were administered for 5 days.
In January 2017, the patient was admitted because of difficulty moving his left arm, headache, and loss of balance for the previous 5 days. On initial examination, he showed left arm paresis and bradypsychia. There were no signs or symptoms of infection. Magnetic resonance imaging (MRI) of the brain showed a focal lesion in the corpus callosum surrounded by oedema and suggestive of lymphoma or glioblastoma (Figure 1); hence, high-dose corticosteroid therapy was prescribed. However, during the first week of admission the patient experienced clinical deterioration and a decrease in level of consciousness. A brain biopsy was performed, with findings of acute and chronic inflammation, abscess formation, and histiocytes containing intracytoplasmatic microorganisms (Figure 2). Chemiluminescence immunoassays (CLI) (Liaison XL Murex) (Malan et al., 2006) and immunochromatography for serological diagnosis of Trypanosoma cruzi were positive, as was the CLIA for Toxoplasma gondii.

Empirical treatment was started with benznidazole, sulfadiazine, and pyrimethamine. The initial benznidazole regimen was 100 mg/8 h, in accordance with the recommended dosage for the treatment of T. cruzi infection (Pierrotti et al., 2018). Real-time PCR (RT-PCR) (Molina et al., 2017; Piron et al., 2007) for the determination of T. cruzi DNA was positive in both blood and brain specimens, whereas RT-PCR for T. gondii was negative in brain; hence, sulfadiazine and pyrimethamine were discontinued. HIV testing was negative. The T. cruzi parasite load, estimated by the amplification cycle threshold (Ct), was higher in the brain biopsy than in the blood sample (12.35 vs. 30.43).

Approximately 2 weeks after receiving the appropriate antiparasitic treatment, the patient’s clinical and neurological status worsened and he required orotracheal intubation. Electroencephalography ruled out non-convulsive status epilepticus, but was consistent with diffuse encephalopathy. A new brain MRI study detected an increase in the size of the Chagas lesion, although RT-PCR analyses for T. cruzi in blood samples were repeatedly negative. In view of this scenario, it was decided to progressively escalate the benznidazole dose up to 300 mg/12 h (15 mg/kg/day) at 24 days after starting this treatment, in order to reach therapeutically effective concentrations in the cerebrospinal fluid (CSF). This amount was well above the recommended dose of 5–10 mg/kg/day (Perin et al., 2017).

After 2 months of treatment with the new dosing regimen (at steady state), blood benznidazole samples were taken at different time points: 1 h, 3 h, 5 h, 8 h, and 12 h after administration. The measured benznidazole concentrations were 14.6 mg/l, 14.8 mg/l, 14.1 mg/l, 10.5 mg/l, and 8.8 mg/l, respectively, all values being above the in vitro trypanosomicidal range (3–6 mg/l) (Raafatuub, 1980). The plasma area under the concentration–time curve from 0 to 12 h (AUC0–12) was 133.2 mg·h/l. In addition, CSF and blood peak (Cmax) samples (3 h after the dose) were taken 2 weeks later. The concentrations achieved were 8.3 mg/l in CSF and 17.2 mg/l in blood, which yielded a CSF/blood Cmax ratio of 48.3% (Figure 3). The patient’s neurological status gradually improved and he was
weaned off orotracheal intubation. A new MRI showed a substantial decrease in the size of the brain mass and oedema. Four RT-PCR T. cruzi parasitemia analyses were conducted at different time points, with negative results; hence, after more than 3 months of benznidazole at 300 mg/12 h, the antiparasitic therapy was discontinued.

Two months after hospital discharge, the patient’s clinical outcome was favourable with functional neurological rehabilitation. His situation was nearly back to normal except for the left arm paresis.

**Discussion**

Information on benznidazole penetration into the CNS is restricted to experimental animal studies, in which the reported mean brain/plasma benznidazole ratio varies considerably from 19% to 68.3%. Furthermore, the permeability of benznidazole through the blood–brain barrier of animals and humans may differ and this remains to be clarified (Perin et al., 2017; Workman et al., 1984). The relatively high concentration measured in the CSF of the patient described here suggests substantial passage of benznidazole through the blood–brain barrier.

The case patient showed good tolerability without the haematological and neurological side effects usually associated with the high doses of benznidazole he received. One study has investigated the relationship between benznidazole plasma concentrations and the development of toxicity (Pinazo et al., 2013). Patients received a dose of 5 mg/kg/day for 60 days, which is much lower than that administered to our patient. Although several cases of toxicity were observed, mainly changes in biochemical parameters and haematological manifestations of bone marrow depression (e.g., neutropenia, thrombocytopenia, anaemia, leukopenia), which resolved after treatment discontinuation, there were no correlations between plasma levels of the drug and these adverse events. It has been reported that plasma benznidazole concentrations below 20 mg/l do not seem to be related to the development of serious adverse events (Pinazo et al., 2013). This is supported by the observations in our patient, whose highest benznidazole plasma concentration was 17.2 mg/dl.

In conclusion, T. cruzi reactivation may occur in immunosuppressed patients; hence, this eventuality should be considered in the differential diagnosis, mainly in patients from endemic areas. This was a challenging case because of the severe presentation and the dearth of available information on benznidazole dosage and the levels achieved in CSF. In conclusion, the experience described suggests that benznidazole can be safely administered in higher doses than those currently recommended for patients showing a torpid evolution, although close monitoring is advisable.

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**Ethical approval**

All procedures were conducted with the full cooperation and adequate understanding of the patient, and have therefore been performed in accordance with the ethical standards of the Declaration of Helsinki.

**Conflict of interest**

The authors declare no conflicts of interest.

**References**


