



Fluconazole-resistant cryptococcal meningitis

To the Editor: Cryptococcal meningitis is a life-threatening mycotic infection common in HIV-positive patients. Amphotericin B and fluconazole are two medications used to treat cryptococcosis in South Africa.¹ Lifelong daily fluconazole prophylaxis after resolution of the primary infection has proved to be effective in preventing relapse.²

Case report

A 40-year-old HIV-positive man was admitted to Cecilia Makiwane Hospital in December 2001 with a history of severe headache, photophobia and fever. Indian ink staining of cerebrospinal fluid (CSF) revealed yeast cells with 3 - 5 budding forms per high-power field. A diagnosis of cryptococcal meningitis was made and the patient was started on amphotericin B. He reacted to this almost immediately, and was observed to have a spiking temperature, tachycardia, and dizziness. He was changed to oral fluconazole 400 mg daily. He improved and was continued on 400 mg of fluconazole for 2 months, and then 200 mg daily.

At subsequent monthly follow-up visits the patient was well. He attended all outpatient appointments, and stated that he was taking treatments as prescribed.

In July 2002 he was readmitted with signs and symptoms of meningitis. CSF examination again revealed budding yeast cells. The patient repeatedly refused the option of amphotericin B because of his previous reaction to this medication. Oral fluconazole was increased to 800 mg per day. The patient's condition continued to deteriorate and he died 2 weeks after admission. Numerous budding forms were still seen on a CSF specimen taken days before his death, and the CSF was cultured.

Cryptococcus neoformans was grown on culture in our laboratory, and the organism was found to be resistant to fluconazole. The organism was sent for minimum inhibitory concentration (MIC) testing but the specimen went astray.

Comment

The prevalence of fluconazole-resistant *C. neoformans* in South Africa is either unknown or poorly publicised. Depending on the resources and protocols available in different centres, treatment may be initiated with amphotericin B, fluconazole, or both.³ However, the fluconazole donation by Pfizer in 2001 has led to more widespread use of this azole as the mainstay of cryptococcosis therapy. Mortality in Zambian AIDS patients with cryptococcal meningitis has been shown to be 100% at 6 months, with or without fluconazole treatment⁴ (median survival with fluconazole 19 days). In patients showing no improvement on fluconazole therapy, culture of CSF, although currently not routinely done, may aid in quantifying the problem of resistant *C. neoformans* in South Africa. Newer azoles with promising activity against *C. neoformans* may help to address this problem in the future, but a case can be made for a national review of resistance patterns. If such information already exists, it would be of benefit to caregivers if it were made public.

**Nancy Momoff
Andrew Parrish**

Department of Medicine
Cecilia Makiwane Hospital
Mdantsane
East London, E Cape

1. Saag MS, Powderly WG, Cloud GA, et al. Comparison of amphotericin B with fluconazole in the treatment of acute AIDS-associated cryptococcal meningitis. *N Engl J Med* 1992; **326**: 83-89.
2. Bozzette SA, Larsen RA, Chiu J, et al. A placebo-controlled trial of maintenance therapy with fluconazole after treatment of cryptococcal meningitis in acquired immune deficiency syndrome. *N Engl J Med* 1991; **324**: 580-584.
3. Maartens G, Regensberg L. HIV-related opportunistic infections. *Modern Medicine of South Africa*, Feb 2000; 42-50.
4. Mwaba P, Mwansa J, Chintu C, et al. Clinical presentation, natural history, and cumulative death rates of 230 adults with primary cryptococcal meningitis in Zambian AIDS patients treated under local conditions. *Postgrad Med J* 2001; **77**: 769-773.