

Fluconazole for the treatment of *Cryptococcus neoformans* meningitis in an immunocompetent host

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ABSTRACT

We present a case of a 23-year-old immunocompetent male who presented with chronic meningitis and was diagnosed as cryptococcal meningitis by positive cryptococcal antigen titer. The cerebrospinal fluid culture was positive for *Cryptococcus neoformans*. He was treated initially with amphotericin B but was later changed to fluconazole due to toxicity. This case highlights the use of fluconazole to successfully treat chronic meningitis in an immunocompetent host.

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Although cryptococcal meningitis (CM) is one of the most common etiologies of fungal meningitis in either immunocompromised or normal hosts, its treatment remains an important challenge. While amphotericin B (alone or in combination with flucytosine) continues to be the standard therapeutic regimen, problems such as a relatively high failure rate, a high incidence of adverse reactions, and the inconvenience of intravenous dosing limits the use of this drug.¹ Fluconazole has proven to be effective for the treatment of CM, but the majority of experience has come from treating CM in patients co-infected with human immunodeficiency virus (HIV).² The current case reports the use of fluconazole to successfully treat CM in an immunocompetent host.

Case Report. A previously healthy 23-year-old Egyptian male was admitted to the hospital with a 2-month history of anorexia and generalized weakness. Two weeks prior to admission, he developed an occipital headache that steadily worsened in severity and 2 days before admission he also developed neck stiffness and projectile vomiting. The patient had no history of repeated infections or hospitalizations and reported no risk factors for HIV. The patient worked as a bus driver

and raised pigeons and chickens at home. On admission his temperature was 37°C, pulse 80 beats/min and blood pressure of 90/60. The patient was thin and appeared moderately ill. He was alert and oriented but he complained of a severe headache. With the exception of nuchal rigidity and a Kerning's and Brudzinski's sign, the physical and neurological exams were normal. Radiographic evaluation of the chest was performed on admission, which demonstrated enlargement of the left hilum along with a small cavity. Admission hemoglobin was 12.9 g/dl, the hematocrit 36.8% and the platelet count 394,000 cells/mm³. The peripheral white blood cell count was 15,100-cells/mm³ with a differential count of 67% neutrophils, 3% band forms, 22% lymphocytes and 8% monocytes. Blood glucose was 62 mg/dl, blood urea nitrogen (BUN) 11 mg/dl, creatinine 0.7 mg/dl, alanine aminotransferase 12 IU/L, aspartate transaminase 12 IU/L and total bilirubin 0.6 mg/dl. An HIV enzyme linked immunosorbent assay (ELISA) test was negative. Admission cerebro-spinal fluid (CSF) analysis revealed 250 cells/mm³ with 61% neutrophils and 39% lymphocytes. The CSF glucose was 5 mg/dl and the protein 92 mg/dl. Gram stain and Ziehl-Nielsen stain of the CSF were negative with subsequent negative cultures for bacteria and mycobacteria. Repeated

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sputum samples were performed and all were negative by stain and culture for fungus and mycobacterium. The initial clinical impression was that the patient had either bacterial or mycobacterial meningitis and he was treated with broad-spectrum antibiotics along with rifampin, isoniazid, pyrazinamide and streptomycin. However, approximately 3 days later, the admission CSF was found to be growing *Cryptococcus neoformans* (*C.neoformans*). An aliquot of the admission CSF was still available and using a commercial kit (Wampole Laboratories, Cranbury, New Jersey, USA), the sample was found to have cryptococcal antigen present at a titer of 1:4224. After the diagnosis of cryptococcal meningitis was made, a contrast enhanced computerized tomography (CT) scan of the brain was performed which showed mild hydrocephalous but no mass lesions, granulomas or abscess formation. At the same time, the antibiotic and anti-tuberculous therapy was discontinued and treatment with amphotericin B was initiated (0.6 mg/kg/day). Lumbar punctures were performed weekly after the diagnosis of *C.neoformans* meningitis was made. The CSF obtained one week after initiation of amphotericin B therapy was still growing cryptococcus and all subsequent CSF cultures were sterile. The cryptococcal antigen was present at a titer of 1:128 in the third week of treatment. The cryptococcal antigen levels remained stable in the CSF at a titer of 1:128 for the next 3 weeks. Additionally, the CSF cell count decreased to 90 cells/mm³ (85% lymphocytes, 15% neutrophils) with a protein of 105 mg/dl and glucose of 57 mg/dl.

While there was improvement in the laboratory values (Table 1), the patient had a complicated clinical course, significantly related to the side effects of amphotericin B. Despite prophylactic administration of steroids, antihistamines and ibuprofen, the patient had fevers to 40°C and uncontrollable rigors with every dose of the amphotericin B. He also developed a generalized tonic/clonic seizure temporally related to administration of amphotericin B, although serum electrolytes, BUN, creatinine and liver enzymes were normal at the time. Mental confusion and hallucinations also occurred in apparent conjunction with administration of the amphotericin.

The persistent side effects experienced by the patient led to the therapy being changed to fluconazole after the patient received a total of 10/mg/kg of amphotericin B. The patient was initially given a 400 mg oral loading dose of fluconazole followed by a daily dose of 200 mg. Within a week of discontinuing the amphotericin B, the patient had no further complaints of fever, chills, seizures or hallucinations. The patient also had a steady increase in his sensorium over the next 2 months but never fully returned to his pre-morbid state. A repeat analysis of the CSF after 10 weeks of treatment with fluconazole demonstrated a cell count of 55 cells/mm³ and a glucose of 43 mg/dl but the protein remained elevated at 174 mg/dl. The cryptococcal antigen in the CSF was 1:2 and the culture of the CSF for cryptococcus was sterile. A repeat contrast enhanced CT scan of the brain demonstrated a significant increase in the hydrocephalous. A ventriculoperitoneal (VP) shunt was placed and within a week the patient experienced a dramatic improvement in his mental status. Three weeks after placement of the VP shunt, fluconazole therapy was discontinued (11 weeks of fluconazole). At the time fluconazole therapy was stopped, the patient had a normal physical exam along with a normal CSF evaluation and the cryptococcal antigen test in the CSF was negative. The patient has been monitored for 12 months since fluconazole was discontinued and he has returned to his normal pre-morbid work schedule and has no complaints related to either the cryptococcal infection or the VP shunt placement.

DISCUSSION. Cryptococcosis has a worldwide distribution with *C.neoformans*, the species typically associated with human disease and commonly found in the soil and areas contaminated by pigeon droppings.³ Not including the present report, only 5 cases of CM have been reported in Egypt since the initial description in 1985.^{4,5} As no systematic studies have been performed, the reason for the paucity of cases reported from the region is unclear. The inability of our patient to tolerate amphotericin B led us to seek alternative therapies. While there has been limited previous

Table 1 - Cerebrospinal fluid values of patient during course of therapy.

CSF values	Baseline	Week One	Week 2	Week 3	Week 4	Week5	Week 6	Week 8	Week 10
CLAT	1/4224	-	-	1/128	1/64	1/128	1/128	1/32	1/2
WBC (10 ³ /ul)	250	430	90	90	0	105	75	100	55
Protein (Mg/dl)	92	130	158	105	50	60	103	105	174
Glucose (Mg/dl)	5	3	17	57	51	42	35	39	43
India Ink Smear	positive	positive	negative						
Culture of <i>cryptococcal neoformans</i>	positive	positive	negative						

CSF - cerebrospinal fluid; CLAT - Cryptococcal Latex Agglutination test; WBC - white blood cells

experience using fluconazole to treat CM in normal hosts, the encouraging data in using the drug to treat CM in patients also infected with HIV provided the rationale to use the drug to treat our patient.³ Fluconazole has many attractive characteristics for treating patients with CM including few reported side effects, good oral absorption which is unaffected by the pH of the gastrointestinal tract, high peak plasma levels with a long terminal half-life, and good penetration into the CSF.^{6,7} In patients with HIV who are co-infected with cryptococcus, fluconazole has been used as an effective consolidation therapy after patients completed initial therapy with Amphotericin B and flucytosine.³ Additionally, fluconazole has been shown to be an effective primary therapy for CM in selected patients with HIV, as well as a prophylactic agent to prevent relapse of CM.³ To date, there has been limited experience using fluconazole to treat CM in HIV negative patients.

In one retrospective, non-randomized study of 60 HIV negative patients, fluconazole appeared to be as effective as amphotericin B for the treatment of CM.⁸ Another study of 19 patients with CM receiving primary therapy with fluconazole resulted in a clinical and mycological response rate of 89%.⁶ A final report of 71 patients with CM found a similar outcome in the 51 patients treated with amphotericin B alone (2-3 gm total dose) as compared to 10 treated with fluconazole alone (400-800 mg intravenously daily for 2 weeks followed by 300-400 mg daily oral therapy) or 10 patients treated for 2 weeks with amphotericin B and then switched to oral fluconazole at a dose of 400 mg daily.⁹ Additionally, patients treated with fluconazole were discharged from the hospital on the average of 36 days earlier than those treated solely with amphotericin B.⁹ Our report supports previous publications reporting the effectiveness of fluconazole for the treatment of CM.

In the present case, we also attempted to use the latex cryptococcal agglutination test as a marker to treatment response. While we were, as were others in the past, able to demonstrate that the decline in antigen titer in the CSF paralleled the improved clinical response of the patient, this has not been a universal finding.^{2,6} Therefore at present, we cannot recommend that treatment be guided by the antigen level in the CSF with the exception that rising antigen levels may be a forewarning of a potential treatment failure. An interesting side observation in our patient was his prolonged abnormal mental status. Initial concerns that the symptom was caused by persistence of the fungus in the CSF was found to be incorrect and actually caused by hydrocephalous with the mental status of the patient returning to normal with the correction of the hydrocephalous. In patients with CM where CT scans of the brains have been performed, hydrocephalous has occurred in 9% to 25% of cases.¹ One study from South Africa reported that 4 of 7 patients with CM who underwent CT scan of the brain had obstructive hydrocephalus.¹⁰ The reason for the frequency of this

complication is not known but may possibly reflect the significant inflammatory response in the subarachnoid space of patients with CM.¹⁰ Treatment of obstructive hydrocephalous in patients with CM often requires placement of a VP shunt. As with our patient, significant or complete reversal of the neurological symptoms is common, especially when the procedure is performed soon after the hydrocephalous is recognized.¹¹ While a common concern, presence of a VP shunt was not associated with spread of cryptococcal infection, did not alter mycological response to therapy and patients rarely required future revisions of their shunt.¹¹

We have demonstrated that fluconazole may be effective for the treatment of cryptococcal meningitis in immunocompetent hosts. The success we report combined with the currently available data suggests that a systematic study of this agent in a controlled setting for the treatment of CM in immunocompetent hosts may be warranted.

Acknowledgment. This research has been conducted in compliance with all Federal Regulations governing the protection of human subjects in research. The opinions and assertions contained herein are the private ones of the authors and are not to be construed as official or as reflecting the views of the Navy Department, Department of Defense, the U.S. Government or the Egyptian Ministry of Health.

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