Treatment of HIV-associated Cryptococcal Meningitis and Central Nervous System Cryptococcoma with Isavuconazole

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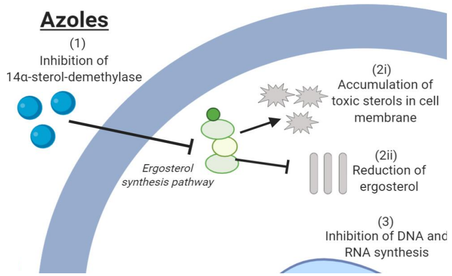
Background

The opportunistic fungal infection cryptococcal meningitis (CM) has a poor prognosis even with treatment. IDSA/BHIVA guidelines recommend amphotericin B and flucytosine induction therapy for 2 weeks.

The efficacy, oral administration and safety profile over prolonged periods of **fluconazole** make it the recommendation for subsequent consolidation and maintenance phases.



Mechanism of azoles against *Cryptococcus*[4]

With increasing fluconazole resistance, alternative antifungals are needed. Itraconazole is less effective than fluconazole and recommended only as second line therapy. Voriconazole's CNS penetration is excellent, but it can be quite toxic and requires close monitoring.

Isavuconazole also penetrates the CNS but is less toxic than voriconazole and so offers promise as an alternative to fluconazole for Cryptococcal Meningitis

Case

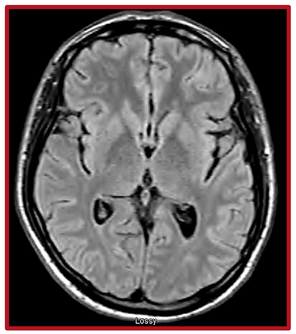
A 39-year-old man from sub-Saharan Africa with uncontrolled HIV presented with a 2-week history of occipital headache, blurred vision, fevers, and malaise. He had no objective neurological deficits. **Serum cryptococcal antigen (CRAG) was positive 1:1280**. MRI Brain excluded a space-occupying lesion.

Lumbar puncture (LP) demonstrated elevated opening pressure (OP) of 25cm H_2O, white cell count of 127 cells/ mm^3 (range 0-5cells/ mm^3, 95% mononuclear) and CSF CRAG 1:160. ***Cryptococcus neoformans*** was cultured.

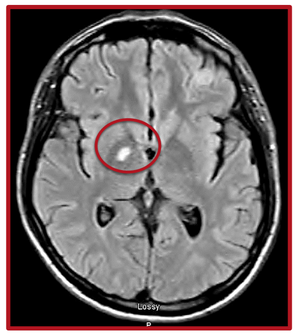
Liposomal Amphotericin-B (LAB) and flucytosine were commenced. Serial LPs were done until OP was 15cm H_2O. Flucytosine was discontinued early due to thrombocytopenia.

	D1	D2	D3	D6
Opening Pressure	25cm H_2O	22cm H_2O	15.5cm H_2O	14.5cm H_2O
Closing Pressure	14cm H_2O	12.5cm H_2O	11.5cm H_2O	13cm H_2O
CSF Removed	10ml	8ml	3ml	3-4ml

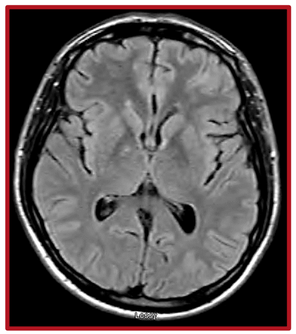
CSF culture was repeated on day 14 and LAB continued until these cultures were confirmed negative (day 21). The ***Cryptococcus neoformans*** isolate had an MIC of 8.0mg/L for fluconazole so 1200mg of fluconazole daily was chosen for consolidation. Antiretroviral therapy started on day 26. By day 34 the patient had developed intractable nausea and vomiting, acute kidney injury, and QT prolongation. MRI Brain FLAIR sequence identified a new cryptococcoma in the setting of IRIS which was treated with LAB re-induction and steroids.



Day 1



Day 55



Day 92

MRI FLAIR changes over time

Image 1: No masses

Image 2: New enhancing mass in the right corpus callosum

Image 3: Improvement in the right corpus callosum mass

Given toxicity with fluconazole, isavuconazole (MIC 0.125mg/L) was chosen as an alternative for consolidation/maintenance and therapeutic drug monitoring was initiated. The cryptococcoma completely resolved radiologically 143 days post discovery. The patient is currently week 32 of therapy with a view to stopping at 1 year.

Discussion

This case illustrates the potential for fluconazole toxicity at high doses and the need for oral alternatives for CM treatment with acceptable safety and tolerability profiles such as isavuconazole.

Barriers to isavuconazole use in resource-limited settings with highest CM incidence include cost, inaccessibility, and the need for therapeutic drug monitoring.

This case demonstrates successful use of isavuconazole in a resource-rich setting for the continuation and maintenance phases of CM management.

References

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