



# Isavuconazole Cerebrospinal Fluid Concentrations in Three Patients with Coccidioidal Meningitis

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## Background

- Isavuconazole has an exceptionally large volume of distribution (155-292 L following oral administration; 304-494 L following intravenous administration).<sup>1,2</sup>
- Minimal human data is available on the penetration of isavuconazole into the cerebrospinal fluid (CSF), but data in mice have demonstrated a CSF/plasma AUC ratio ~1.8:1.<sup>3</sup> A brain tissue concentration of 1.46 mg/kg was found in a patient with cerebral aspergillosis.<sup>4</sup>
- A small case series support its use in salvage therapy for coccidioidal meningitis.<sup>5</sup>
- At our center, isavuconazole was initiated at standard dosing for salvage therapy to treat coccidioidal meningitis in three patients.

## Methods

- Paired CSF and plasma isavuconazole concentrations were measured at times that corresponded with planned procedures (e.g. lumbar puncture, Ommaya placement)
- CSF samples were acquired via lumbar puncture (LP), external ventricular drain (EVD), or Ommaya reservoir.
- All samples were tested via UPLC/MS at the University of Texas Fungus Testing Laboratory.

## Cases

- Patient 1 is a previously healthy 66-year old male initiated on isavuconazole after progressive symptoms on fluconazole, voriconazole, liposomal amphotericin B, and intrathecal amphotericin B.

Day	Route	Plasma µg/mL (hrs post-dose)	CSF µg/mL (hrs post-dose)
<b>Patient 1</b>			
9	IV	2.6 (24.8)	--
11	IV	1.96 (2)	<0.25 (2, EVD)
12	IV	1.49 (23)	<0.25 (23, EVD)
15	IV	1.78 (24.6)	0.45 (14.5, LP)
15	IV	--	<0.25 (24.6, EVD)
25	PO	1.25 (23.5)	<0.25 (23.5, Ommaya)
25	PO	3.08 (2.3)	<0.25 (2, Ommaya)
44	PO	1.8 (22.3)	0.69 (22.9, LP)
<b>Patient 2</b>			
6	IV	3.02 (5.7)	<0.25 (5.8, EVD)
<b>Patient 3</b>			
9	PO	3.3 (23.5)	--
10	PO	6.38 (2.7)	<0.25 (2.7, Ommaya)
11	PO	5.06 (24.5)	1.15 (24.5, LP)
42	PO	5.63 (7.5)	1.72 (6.5, LP)

## Conclusions

- Isavuconazole CSF concentrations collected via lumbar puncture resulted in mean CSF:plasma ratio of 0.31 (range 0.23-0.38) with concentrations ranging 0.45-1.72 µg/mL.
- No detectable isavuconazole CSF concentrations were observed when CSF was obtained via EVD or Ommaya reservoir.

## Cases (cont'd)

- Paired isavuconazole levels were drawn on multiple days (range 9-44). Plasma concentrations ranged from 1.49-3.08 µg/mL with corresponding lumbar puncture CSF concentrations 0.49-0.69 µg/mL. All ventricular samples (Ommaya, EVD) were undetectable.
- Patient 2 is a previously healthy 33 year-old woman initiated on isavuconazole after failing high-dose fluconazole, liposomal amphotericin B, and intrathecal amphotericin B.
- A single set of paired isavuconazole concentrations were collected in plasma (3.02 µg/mL) and CSF (<0.25 µg/mL) via EVD.
- Patient 3 is a previously healthy 22 year-old man initiated on isavuconazole after therapeutic failure or toxicity on multiple prior antifungal therapies (fluconazole, voriconazole, posaconazole, liposomal amphotericin B, and intrathecal amphotericin B).
- Paired isavuconazole levels were drawn on three occasions (days 10-42), plasma concentrations ranged 5.06-6.38 µg/mL (note timing of levels) with lumbar puncture CSF concentrations ranging from 1.15-1.72 µg/mL. A single CSF sample taken from the patient's Ommaya reservoir yielded an undetectable isavuconazole concentration.

## References

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