

Case study: Invasive Histoplasmosis

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Spectrum

Yeast

Dimorphic fungi

Aspergillus species

Onychomycosis

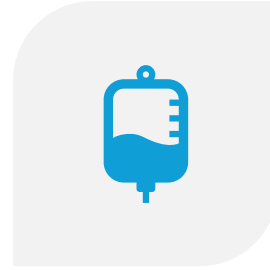
Four formulations



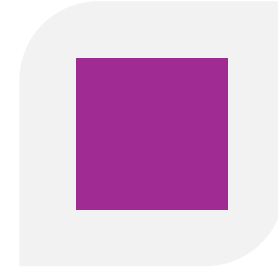
SUSPENSION



CAPSULE



INTRAVENOUS
FORMULATIONS



SUBA
ITRACONAZOLE

Itraconazole: Pharmacokinetic

- Exhibits highly variable and non-linear pharmacokinetics
 - Gastric acidity improves absorption of itraconazole (capsules)
 - Capsules to be administered with food and with acidic beverage (e.g. cola)
 - Solution should administered on empty stomach –food reduces absorption by 30%
- Solution and capsules are not bioequivalent and not interchangeable
- Solution has 30% higher oral bioavailability than capsules
- Itraconazole is widely distributed throughout the body
 - Very high concentrations of itraconazole and / or its metabolites are found in skin, lungs, muscle and liver

Itraconazole: Pharmacokinetic

- Itraconazole undergoes oxidative metabolism, primarily by the CYP3A4 isoenzyme
- Itraconazole and its metabolites significantly inhibit CYP3A4
 - CYP3A4 inhibition contributing to the increased bioavailability of its own over a time
- First metabolite hydroxyitraconazole is about 1.5–2 times the levels of the parent drug
- An elimination half-life of 20 h after a single dose of 200 mg
- Itraconazole accumulates slowly

Itraconazole

- Loading dose 200mg q8h X 3 days followed by 200mg q12h
- Steady state level target trough concentrations are only reached after 7–15 days of dosing
- TDM of itraconazole performed after the first week of therapy
 - At regular intervals (e.g. every 1–2 weeks) according to the clinical context (e.g. when interacting drugs are started or discontinued)

SUBA (super bioavailable) Itraconazole

- Novel formulation designed to enhance the bioavailability
- SUBA-itraconazole bioavailability is approximately 173% of that of capsule with 21% less interpatient variability
- Releases the drug in the duodenum, enhancing absorption
- Food intake has a modest effect on SUBA-itraconazole
- Drug can be taken with or without food
 - Under fed conditions, the total and peak exposure of itraconazole are slightly lower compared to the fasted state
- Proton pump inhibitors (omeprazole) increases itraconazole AUC by 22% and the C_{max} by 31%

SUBA (super bioavailable) Itraconazole

- SUBA-itraconazole (6 days) achieves rapid therapeutic level compared to the itraconazole (14 days)
- Less interpatient variability than conventional itraconazole
- 69% of patients in the SUBA group achieved therapeutic level compared to only 21% in the itraconazole at day 10
- ***Enhanced bioavailability and more consistent drug levels of SUBA contribute to its superior efficacy***

Itraconazole dosage in organ impairment

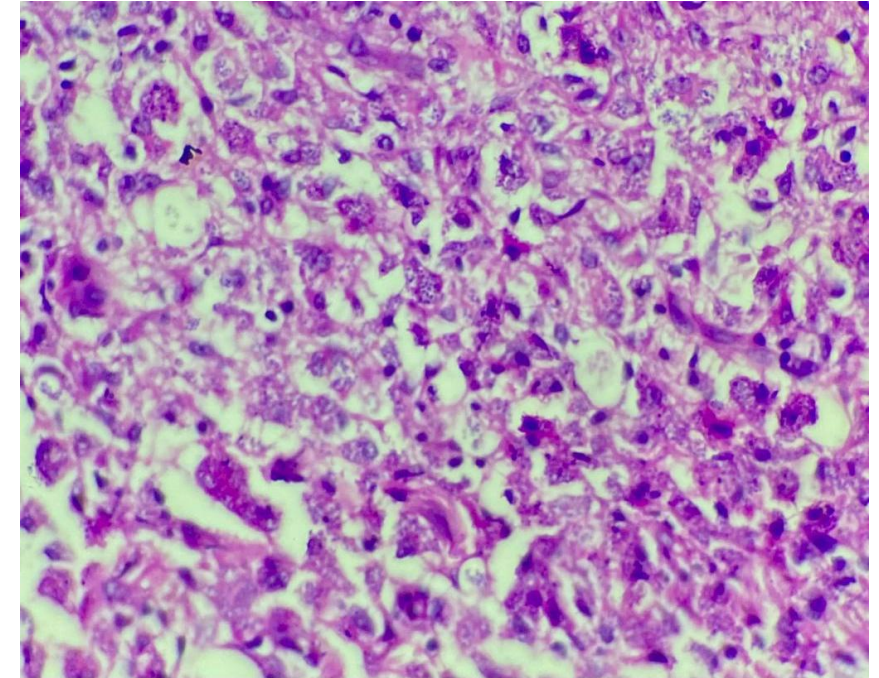
- **Liver Impairment:** Absorption and elimination of itraconazole affected; requires dosage individualization
- **Renal Impairment:** IV preparation contains cyclodextrin and individuals with a creatinine clearance under 30 mL/min, probably because of the impaired renal excretion of metabolites and cyclodextrin
- **Cardiac failure:** avoid in CHF patients: ITR is negative inotrope and can precipitate heart failure

Case scenario

- 73/Male, residing at Banswara, Rajasthan, Farmer, No travel History, on antihypertensive
- Well before 3 months
- Cough, Progressive weight loss (18 kg), weakness
- Difficulty in chewing for last two months
- Nodular skin lesions started from the forehead, rapidly progressive & involve entire forehead, face, limbs, back and right axillae for last 1 month
- Fever for last 10 days



- Patient was worked up at other hospital with CT scan showing two small pleural based nodules rest unremarkable
- HIV/HBsAg Non-reactive
- Skin Biopsy:
- Referred to our clinic,
- Physical Exam:
 - Vitals: 104/58 (postural hypotension with 6 mm fall)
 - **Multiple nodular lesions in gums**
 - **Firm hepatosplenomegaly (Liver 5 fingers and spleen 4 fingers below the costal margin)**
- L-AmB 3mg/kg/day along with Cap Itraconazole 200mg TDS X 3 days followed by 200mg BID started
- Adrenal support: Prednisolone 5mg 1 – 0.5 - 0
- Patients had a great clinical response at 2 weeks



Itraconazole trough level after 8 days

	Day 8 ITR 200mg TDS X 3 days Followed by 200mg BID				
Itraconazole µg/ml	0.064				
Hydroxy- itraconazole µg/ml	0.19				
Total µg/ml	0.25				

Itraconazole TDM:

- Timings: 7 -10 days
- Goal levels: Levels ≥ 1 mcg/ml have been associated with treatment success
- Increased risk of Toxicity: Not well defined, but concentrations > 5 mcg/ml
- Measure both itraconazole and hydroxy-itraconazole and should be considered when assessing drug levels

Antifungal dose adjustment considerations according to TDM

Itraconazole	
Drug Level (mg/L)	Consider Dose Adjustments
Supratherapeutic: >3-4	Consider dose reduction if the patient is experiencing an adverse event (or transition to another antifungal if clinically appropriate).
Therapeutic: 0.5 to 3-4 (depending on indication)	No change
Subtherapeutic: <0.5 –1 (depending on indication)	<ul style="list-style-type: none">• For capsules, absorption can be increased by taking the medication with an acidic carbonated beverage (such as cola or ginger ale) or stopping or reducing H2RAs and PPIs• Change capsules to solution• Increase daily dose by 100-200 mg• For solution, take the medication on an empty stomach

Case continued

	Day 8 ITR 200mg TDS X 3 days Followed by 200mg BID	day 12 ITR SUBA 300mg BID			
Itraconazole µg/ml	0.064	0.23			
Hydroxy- itraconazole µg/ml	0.19	0.21			
Total µg/ml	0.25	0.44			

Case continued

	Day 8 ITR 200mg TDS X 3 days Followed by 200mg BID	day 12 ITR SUBA 300mg BID	Day 16 ITR SUBA 300mg BID		
Itraconazole µg/ml	0.064	0.23	0.41		
Hydroxy- itraconazole µg/ml	0.19	0.21	0.47		
Total µg/ml	0.25	0.44	0.88		

Case continued

	Day 8 ITR 200mg TDS X 3 days Followed by 200mg BID	day 12 ITR SUBA 300mg BID	Day 16 ITR SUBA 300mg BID	Day 21 Posacon- azole	
Itraconazole µg/ml	0.064	0.23	0.41		
Hydroxy- itraconazole µg/ml	0.19	0.21	0.47		
Total µg/ml	0.25	0.44	0.88	< 0.25	

Itraconazole trough level after 7 days

	Day 8 ITR 200mg TDS X 3 days Followed by 200mg BID	day 12 ITR SUBA 300mg BID	Day 16 ITR SUBA 300mg BID	Day 21 Posacon- azole	Day 30 ITR SUBA 300mg TID
Itraconazole µg/ml	0.064	0.23	0.41		0.43
Hydroxy- itraconazole µg/ml	0.19	0.21	0.47		1.0
Total µg/ml	0.25	0.44	0.88	< 0.25	1.43

Case continued

- Clinical exam: Complete regressions in hepatosplenomegaly, marked reduction in skin nodules at 2 months treatment
- Feeling much better with weight gain
- His adrenal support was discontinued

Case continued

- Patient completed 4 months on antifungal, gums lesions improved and started eating/chewing food
- After 1 month
 - Complaining of weakness, became hypertensive, requiring antihypertensives
 - Laboratory report: Na: 140, K: 2.8, Mg: 1.2, CBC, LFT, Creatinine within normal limit

What's going on

- Worsening adrenal insufficiency
- Disease progression
- Cardiac event

What will you do next?

1. Check Renin-Aldosterone level
2. Check serum cortisol and ACTH
3. Check Itraconazole trough level
4. ECG and Echocardiography
5. All of the above

Case continued

- Magnesium and K correction was prescribed
- No response, persistent hypokalemia – refractory hypokalemia
- ITR trough level: 12.4 mg/L
- Managed by holding ITR for four days and restarting 200mg BID
- ITR levels reaches to 2.1 mg/L after 4 weeks
- Normalization of electrolytes with clinical improvement

Itraconazole associated pseudo-hyperaldosteronism

- Mimics primary hyperaldosteronism but without elevated aldosterone levels
 - Hypertension
 - Hypokalemia
 - Metabolic alkalosis
 - Low plasma renin activity
 - Low aldosterone levels
- Mechanism: Inhibition of the enzyme 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) by itraconazole
- This enzyme converts active cortisol to its inactive form, cortisone, in the kidneys
- Cortisol accumulates with inhibition of 11 β -HSD2, and activates mineralocorticoid receptors, leading to sodium retention, potassium excretion, hypertension and hypokalemia

Risk group

- Patients receiving prolonged antifungal therapy – for histoplasmosis, blastomycosis, and aspergillosis
- Dose dependent side effect: higher itraconazole serum levels are more likely to associated
- High-dose itraconazole (600 mg daily) was associated with the higher incidence of hypertension (31%; 6.9% grade 3) and hypokalemia (17.2%; 10.3% grade 3) compared with 0% with low dose (200 mg daily) in a randomized trial
- TDM and dose adjustments will help in managing and preventing this ADR

Take home points

- Itraconazole solution is 30% more bioavailable than capsule
- SUBA-Itraconazole markedly improves PK-PD parameters
- Itraconazole & hydroxy-itra are strong inhibitors of CYP3A4
- Frequent TDM for Itraconazole is advisable especially in patient requiring prolong therapy



Thank You