Posaconazole and Itraconazole Induced Hypertension and Hypokalemia:
Mechanism and Treatment Implications

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DISCLOSURES

Name of Organization	Relationship
Pfizer, Merck, Astellas, Wako, Scynexis, Cidara, Vical, T2, F2G	Research Support
Astellas, Vical, Cidara	Consulting

Coccidioidomycosis: Treatment

Primary treatment:

- Fluconazole
- Itraconazole

Refractory to treatment or adverse effects:

- Posaconazole
- Voriconazole
- Isavuconazole

Triazole Adverse Events

Voriconazole

- Visual disturbance: reversible dysfunction of retinal ON-bipolar cells
  Kinoshita J, et al. *Invest Ophthalmol Vis Sci* 2011; 52: 5058-63.
- Cutaneous effects and malignancy: VORI and N-oxide are UVA-sensitizers
  Ona-Vu K, et al. Br J Dermatol. 2015; 173(3):751-759.
- Fluorosis: cleavable fluoride residue Wermers RA et al. *Clin Infect Dis* 2011; 52: 604-11.

Isavuconazole **??**

Fluconazole

- Alopecia, xerosis, cheilitis, nausea, anorexia: mechanism unknown

Itraconazole

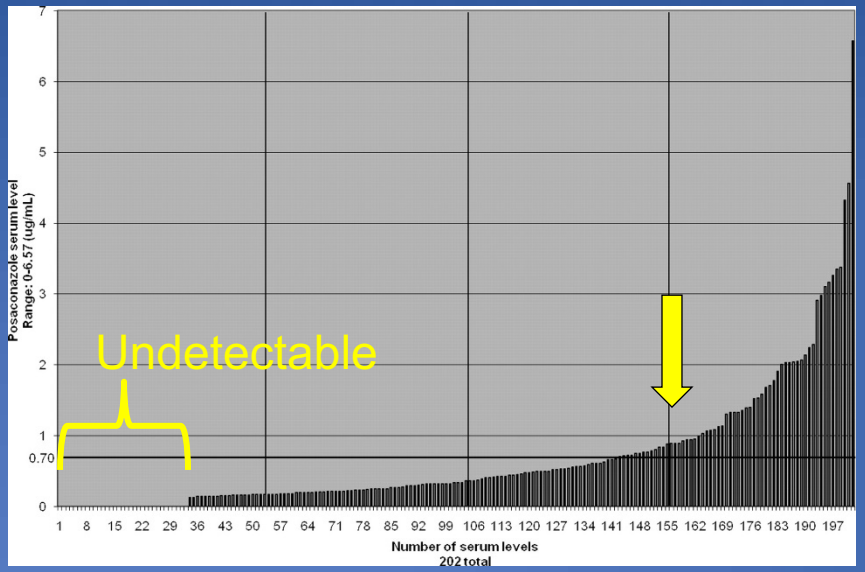
- Oral administration: GI - oral solubilizing agent
- Negative Inotrope: inhibition of cardiac NaV channel, directly myotoxic, precise mechanism unknown Qu Y, et al. *Toxicol Appl Pharmacol* 2013; 268: 113-22

Posaconazole

- Few side effects with suspension (taste), however changes in formulation over last few years have increased drug exposure

Posaconazole solution:

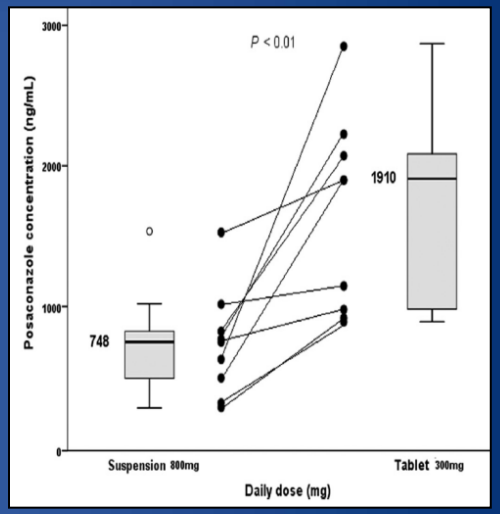
~75% of all samples below recommended/target serum concentration



Posaconazole Tablet:

Improved serum [conc] (median of 0.74 → 1.92 µg/mL)

- ~10% still with levels < 0.7



- 10% with levels > 3.5 µg/mL
- Ceiling for toxicity?

Thompson GR, et al. ***Antimicrob. Agents Chemother***. 2009;53:2223-2224
Jung DS, et al. ***Antimicrob. Agents Chemother.*** 2014;58(11):6993-5.

Posaconazole and HTN

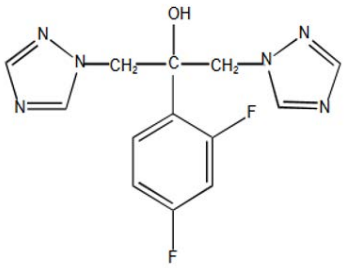
Patient 1

- 67 y/o WM with chronic cavitary aspergillosis - no prior hypertension.
- Intake labs within normal limits; K = 4.1 mmol/L). Posaconazole tablets were started (300 mg twice daily on day 1, followed by 300 mg daily).
- 35 days later, blood pressure 165/89 mmHg. Potassium decreased to 3.4 mmol/L; **serum posaconazole 4.36** µg/mL.

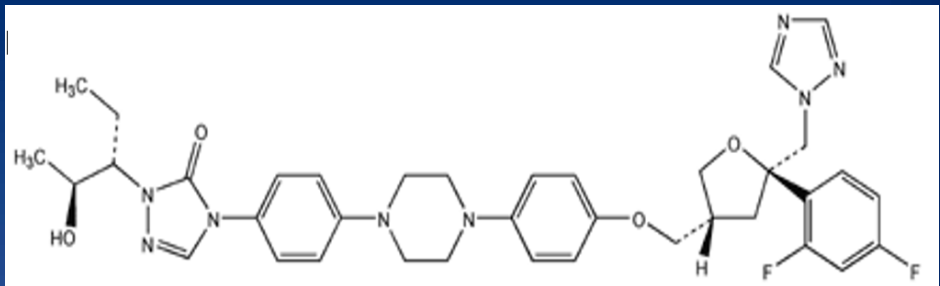
Patient 2

- 59 y/o AAM with chronic pulmonary coccidioidomycosis - no prior hypertension started on posaconazole 300 mg daily
- Three months later BP to 196/114 mm Hg. Baseline labs normal; **posaconazole level 4.6 µg/mL.**

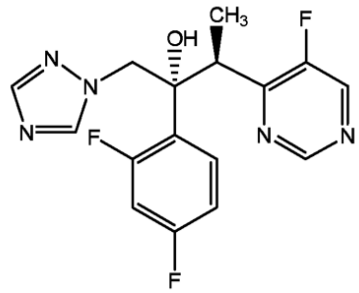
		Renin (0.25 – 5.82 ng/mL/h)	Aldosterone (3-16 ng/dL)	11-deoxycortisol (≤42 ng/dL)	Estradiol (<39 pg/mL)
Patient 1	**Intake**	**0.11**	**<1**	**177**	**48**
	21 days after stopping	1.34	4	36	35
	100 mg POSA	2.47	3	<20	26
Patient 2	**Intake**	**0.1**	**<1**	**335**	76
	28 days after stopping	0.76	**<1**	33	**51**
	100 mg POSA	1.34	6	<20	27



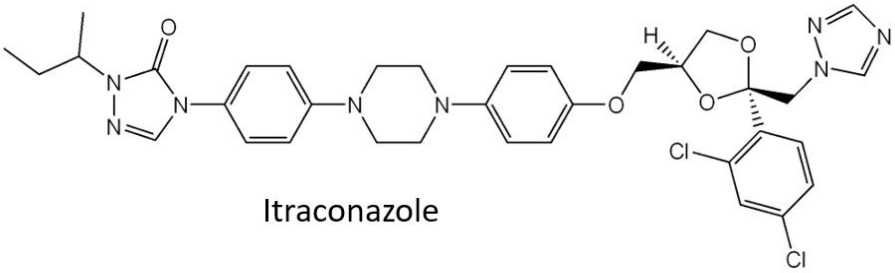
Fluconazole



Posaconazole

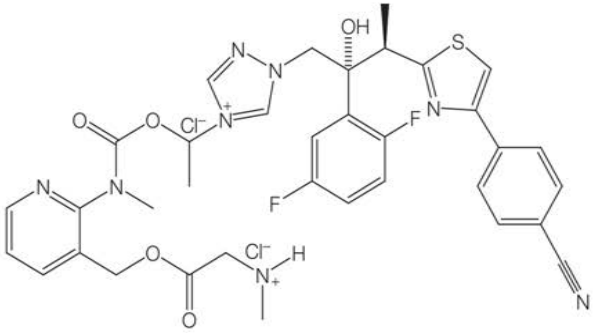


Voriconazole

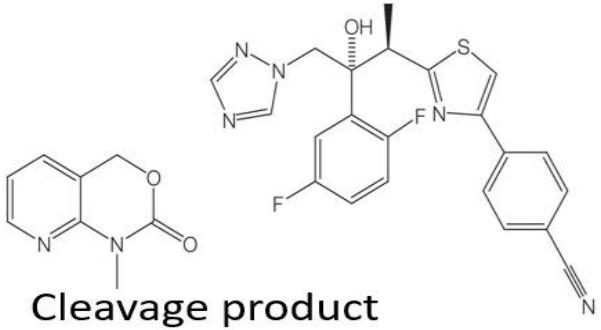


Itraconazole

Isavuconazole



Isavuconazonium (pro-drug)



Cleavage product

Itraconazole and HTN

Patient 3

- 59 y/o WM with disseminated coccidioidomycosis (T12 vertebral lesion); treated with fluconazole 400 daily
- Normal blood pressure and labs initially. Due to dry skin patient changed by outside provider to **itraconazole 300 mg twice daily**
- Over next 4 months becomes progressively more hypertensive.
  - Itraconazole: 2.11 µg/mL
  - Hydroxyitraconazole: 2.83 µg/mL
    - Past publications- itraconazole serum levels (capsules): 0.297-1.609 (median 0.741 µg/mL)

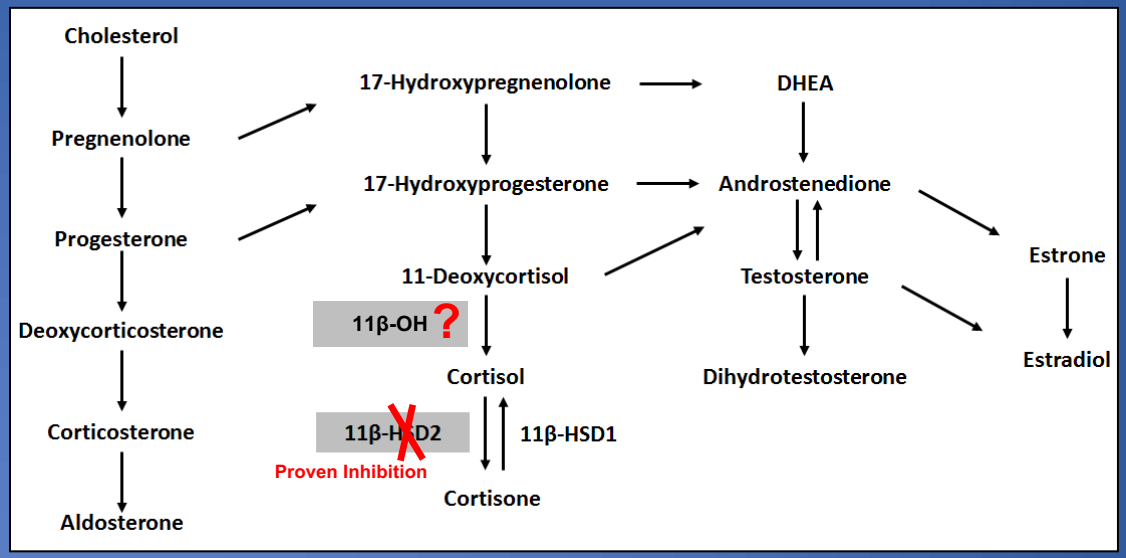
		Renin (0.25 – 5.82 ng/mL/h)	Aldosterone (3-16 ng/dL)	11-deoxycortisol (≤42 ng/dL)	Estradiol (<39 pg/mL)
Patient 3	Intake	**0.13**	**1**	**55**	**40**
	30 days after change to VORI 200 BID	0.69	4	27	26

Enzyme Inhibition

Recognition of 3 patients: Hypertension, hypokalemia, alkalosis

All had posaconazole levels >4 µg/mL; elevated itraconazole levels

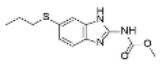
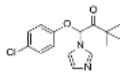
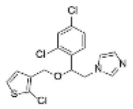
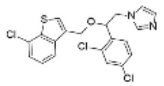
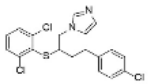
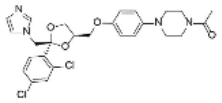
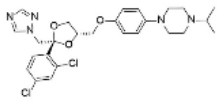
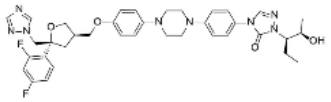
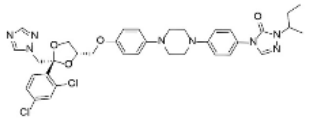
Undetectable renin and aldosterone
Elevated 11-deoxycortisol, and cortisol/cortisone ratio



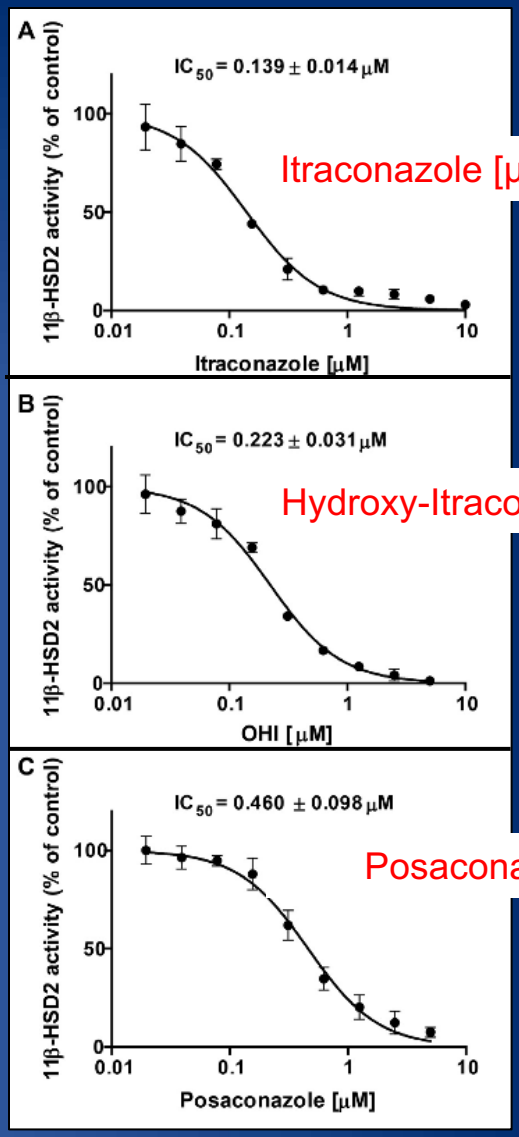
11β-OH, 11 β -hydroxylase
11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1 and type 2

Inhibition Historically:

- Black licorice (glycyrrhetinic acid)
- Carbenoxolone
- Grapefruit juice/flavonoids

compound	structure	residual enzyme activity [% of control] (20 µM)		IC_{50} values [µM]	
		11β-HSD1	11β-HSD2	11β-HSD1	11β-HSD2
Albendazole		105 ± 5	100 ± 15	n.d.	n.d.
Climbazole		57 ± 10	86 ± 12	n.d.	n.d.
Tioconazole		18 ± 3	44 ± 5	4.97 ± 0.64	n.d.
Sertaconazole		35 ± 3	61 ± 5	12.73 ± 1.69	n.d.
Butoconazole		48 ± 6	50 ± 6	n.d.	n.d.
Ketoconazole		67 ± 4 [a]	26 ± 2 [a]	n.d.	n.d.
Terconazole		97 ± 6	62 ± 5	n.d.	n.d.
Posaconazole		88 ± 11	8 ± 5	n.d.	0.460 ± 0.098
Itraconazole		89 ± 6	4 ± 3	n.d.	0.139 ± 0.014

Percent inhibition and IC_{50} of azole inhibition of 11β-HSD1 and 11β-HSD2



Inhibition of 11β-HSD2 in cell lysates

Adverse Events – Package Insert

Itraconazole

- Solution & Capsules: hypokalemia (2%), hypertension (3%)
- High-Dose Itraconazole (600mg/day)
  - Hypokalemia and hypertension 5/8 patients
    - Serum levels > 5 µg/mL in all 5/8 by bioassay

Posaconazole

- Intravenous: Hypokalemia (22%), Hypertension (8%)
- Solution: Hypokalemia (33%), Hypertension (18%)
- Tablet: Hypokalemia (22%), Hypertension (11%)

Sharkey PK, et al. ***Antimicrob. Agents Chemother***. 1991; 35(4):707-13.

Conclusions

Posaconazole and Itraconazole Induced Hypertension, Hypokalemia and alkalosis (AME syndrome)

- Essential role for 11β-HSD2 inhibition
- Role of 11β-hydroxylase inhibition as contributory pathway?

Dose-reduction and alternative triazoles both effective in ameliorating AME syndrome

- **What is the incidence?**
- **Investigation of other triazoles?**
  - Fluconazole, Voriconazole, Isavuconazole?
- **Genetic polymorphisms responsible?**
  - Very little heterogeneity in these enzymes
- **Definitive serum drug level association?**

Thank You!

UC-Davis

- Ian McHardy PhD
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University of Basel

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- Murielle Bachler PhD
- Katharina Beck PhD

Thank You!

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