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

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## DISCLOSURES

<table>
<thead>
<tr>
<th>Name of Organization</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer, Merck, Astellas, Wako, Scynexis, Cidara, Vical, T2, F2G</td>
<td>Research Support</td>
</tr>
<tr>
<td>Astellas, Vical, Cidara</td>
<td>Consulting</td>
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</tbody>
</table>
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
  
- Cutaneous effects and malignancy: VORI and N-oxide are UVA-sensitizers
  
- Fluorosis: cleavable fluoride residue
  

**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
  

**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

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**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?

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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.

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

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<thead>
<tr>
<th></th>
<th>Renin</th>
<th>Aldosterone</th>
<th>11-deoxycortisol</th>
<th>Estradiol</th>
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<tbody>
<tr>
<td></td>
<td>(0.25 – 5.82 ng/mL/h)</td>
<td>(3-16 ng/dL)</td>
<td>(&lt;42 ng/dL)</td>
<td>(&lt;39 pg/mL)</td>
</tr>
<tr>
<td>Patient 3 Intake</td>
<td>0.13</td>
<td>1</td>
<td>55</td>
<td>40</td>
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<tr>
<td>30 days after change to VORI 200 BID</td>
<td>0.69</td>
<td>4</td>
<td>27</td>
<td>26</td>
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</tbody>
</table>
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

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

11β-OH, 11 β-hydroxylase
11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1 and type 2
<table>
<thead>
<tr>
<th>compound</th>
<th>structure</th>
<th>residual enzyme activity [% of control] (20 µM)</th>
<th>IC50 values [µM]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>11β-HSD1</td>
<td>11β-HSD2</td>
</tr>
<tr>
<td>Albendazole</td>
<td><img src="image" alt="Albendazole Structure" /></td>
<td>105 ± 5</td>
<td>100 ± 15</td>
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<tr>
<td>Climbazole</td>
<td><img src="image" alt="Climbazole Structure" /></td>
<td>57 ± 10</td>
<td>86 ± 12</td>
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<tr>
<td>Tioconazole</td>
<td><img src="image" alt="Tioconazole Structure" /></td>
<td>18 ± 3</td>
<td>44 ± 5</td>
</tr>
<tr>
<td>Sertaconazole</td>
<td><img src="image" alt="Sertaconazole Structure" /></td>
<td>35 ± 3</td>
<td>61 ± 5</td>
</tr>
<tr>
<td>Butoconazole</td>
<td><img src="image" alt="Butoconazole Structure" /></td>
<td>48 ± 6</td>
<td>50 ± 6</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td><img src="image" alt="Ketoconazole Structure" /></td>
<td>67 ± 4a</td>
<td>26 ± 2a</td>
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<tr>
<td>Terconazole</td>
<td><img src="image" alt="Terconazole Structure" /></td>
<td>97 ± 6</td>
<td>62 ± 5</td>
</tr>
<tr>
<td>Posaconazole</td>
<td><img src="image" alt="Posaconazole Structure" /></td>
<td>88 ± 11</td>
<td>8 ± 5</td>
</tr>
<tr>
<td>Itraconazole</td>
<td><img src="image" alt="Itraconazole Structure" /></td>
<td>89 ± 6</td>
<td>4 ± 3</td>
</tr>
</tbody>
</table>

Percent inhibition and IC50 ofazole inhibition of 11β-HSD1 and 11β-HSD2 in cell lysates.

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%)

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!

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- Wesley Hoffman PharmD
- Alison Semrad MD

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- Murielle Bachler PhD
- Katharina Beck PhD
Thank You!

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