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Itraconazole Induced Hypertension and Hypokalemia: Mechanistic Evaluation

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ABSTRACT

We describe a case of apparent mineralocorticoid excess (hypertension, hypokalemia, metabolic alkalosis, and low plasma renin activity) secondary to itraconazole therapy. Inhibition of 11β-hydroxysteroid dehydrogenase 2 was demonstrated, and withholding itraconazole led to resolution of adverse effects that did not recur with voriconazole. This report adds to a growing body of evidence linking apparent mineralocorticoid excess with certain triazoles.

Itraconazole is a broad spectrum triazole antifungal agent. In addition to its indications for refractory aspergillosis and onychomycosis this agent is considered a first-line agent in the treatment of coccidioidomycosis [1]. Itraconazole has variable bioavailability with significant differences between the capsule and solution formulations, as well as administration in the fasting versus fed state [2]. The efficacy of itraconazole has been associated with serum drug concentrations and given its erratic absorption, therapeutic drug monitoring of itraconazole is generally recommended [3]. Conversely, toxicity of itraconazole has not been associated with serum drug levels although hypertension and hypokalemia appear more common with higher itraconazole dosing strategies [4]. We report a case of apparent mineralocorticoid excess syndrome (AME) secondary to itraconazole and describe the molecular mechanism responsible.

A 59-year-old man with a history of hyperlipidemia and osteoarthritis presented to an outside clinic with a diagnosis of disseminated coccidioidomycosis (T12 vertebral lesion). Upon diagnosis, he was initiated on fluconazole 400 mg daily, which was later increased to 800 mg daily. Over the following two months the patient exhibited normal vital signs (blood pressure between 110-134/62-70 mm Hg), but complained of increasingly severe dry skin

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and the patient was subsequently changed to itraconazole 300 mg PO twice daily by an outside provider. At initiation of therapy his chemistry profile was normal (serum potassium 4.3 mmol/L). One month after starting itraconazole therapy, the patient presented to his primary care physician, noting the new onset of elevated home blood pressures (between 140-160/80-100 mm Hg). On this clinic visit, the patient's blood pressure was 143/81 mm Hg. Follow up visit 3 months later revealed that his blood pressure remained significantly elevated (132-180/74-93 mm Hg) with a normal heart rate. His primary care physician prescribed metoprolol succinate 25mg daily, without a subsequent reduction in his blood pressure. Repeated measurement demonstrated that the patient was consistently between 150-188/70-97 mm Hg which was similar to the patients reported home blood pressure monitoring. Repeat chemistry profile at this time exhibited a decline in his potassium level to 3.8 mmol/L. The serum itraconazole and hydroxyitraconazole concentrations were 2.11 µg/mL and 2.83 µg/mL (determined by UPLC/MS) respectively and he was referred to our center for assistance in management (other endemic mycoses have targeted a serum itraconazole level > 1 µg/mL) [5].

Upon referral, additional workup was initiated on suspicion of the apparent mineralocorticoid excess (AME) syndrome secondary to high-dose itraconazole therapy (Table 1). These results exhibited suppression of plasma renin and aldosterone (0.13 ng/mL/h and <1 ng/dL respectively) an elevation of 11-deoxycortisol level (55 ng/dL), a mildly elevated estradiol level (40 pg/mL) and a serum potassium of 3.4 mmol/L. No dietary source consistent with AME (licorice etc) were identified on review with the patient. At this time itraconazole was discontinued and the patient placed on voriconazole 200 mg twice daily with subsequent resolution of his hypertension, electrolyte, and endrocrinologic abnormalities over the following 4 weeks.

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The adverse effects from itraconazole induced disruption of the steroid biosynthesis pathway have been speculated in prior reports evaluating high-dose itraconazole therapy [4]. Other reports have similarly described hypertension as a side-effect of itraconazole therapy although the pathophysiologic processes responsible in these prior publications was not elucidated [6-8]. Our patient's laboratory results show 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) inhibition as evidenced by the suppression of renin and aldosterone and deoxycorticosterone in combination with elevated 11-deoxycortisol levels and the resultant increase in estradiol serum levels – all findings consistent with the recent description of *in vitro* suppression of 11β-HSD2 by itraconazole [9] and a recent clinical report showing the AME syndrome with the structurally related triazole posaconazole [10]. It is important to note this syndrome is frequently observed with normal serum cortisol levels, and it is the ratio of cortisol to cortisone responsible for the observed adverse effects [11].

The kidney isoform of 11β-HSD2 serves the critical homeostatic regulatory function of dampening mineralocorticoid activity by converting cortisol to cortisone, which, unlike cortisol, lacks mineralocorticoid receptor affinity (Figure 1) [12]. Thus, in the absence of functional 11β-HSD2, even a normal plasma cortisol can overwhelm mineralocorticoid receptors, resulting in reduction of both renin and aldosterone levels [11, 13]. A recent in-vitro study found the 50% inhibitory concentration (IC_{50}) of itraconazole was 139 +/- 14 nM and 223 +/- 31 nM for hydroxyitraconazole for 11β-HSD2 (which is exceeded by most patient serum concentrations). The type 1 isoform of 11β-hydroxysteroid dehydrogenase mediates the reverse (conversion of cortisone to cortisol), but exhibits low overall sequence identity (18%) with the type 2 isoform and, accordingly, is much less sensitive to inhibition by azole compounds *in-vitro* [9].

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Itraconazole has been associated with hypertension in clinical reports previously, however there has not been a theoretical mechanism proposed for these findings. Similar to the previously cited report of posaconazole, our case reveals a mechanism and demonstrates probable causality by resolution following a change in antifungal therapy to the structurally non-related triazole voriconazole. This report allows for itraconazole to be included, along with posaconazole, to the list of other medications/products (e.g. licorice, carbenoxolone, grapefruit juice) that lead to acquired deficiency of 11β-hydroxysteroid dehydrogenase [14, 15].

In summary, itraconazole therapy was found associated with 11β-hydroxysteroid dehydrogenase type 2 inhibition and new onset hypertension. Prior studies have shown a low incidence of hypertension (3%) and hypokalemia (2%) with standard itraconazole dosing (400 mg total daily dosing) [16], however higher doses (600 mg total daily dosing) have found a much higher incidence of these adverse effects suggesting possible dose-dependent toxicity (63% of patients developed hypertension and hypokalemia) [4]. It is unclear what the frequency of this complication of antifungal therapy is, and larger studies are needed to assess this adverse effect. It is also unclear if there are specific polymorphisms that predispose patients to this syndrome. Identification of this adverse effect in a patient can reasonably be accomplished by a review of a patient's blood pressure and serum potassium, with further work-up necessary only with a change in pretreatment values.

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Figure and Table Legend

Table 1. Evaluation of patient with new onset hypertension after initiation of itraconazole therapy.

Figure 1. Itraconazole induced inhibition of 11β-HSD2 results in a build-up of precursor hormones causing the apparent mineralocorticoid excess syndrome.

Figure 1 footnote: 11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2

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Table 1. Evaluation of patient with new onset hypertension after initiation of itraconazole therapy.

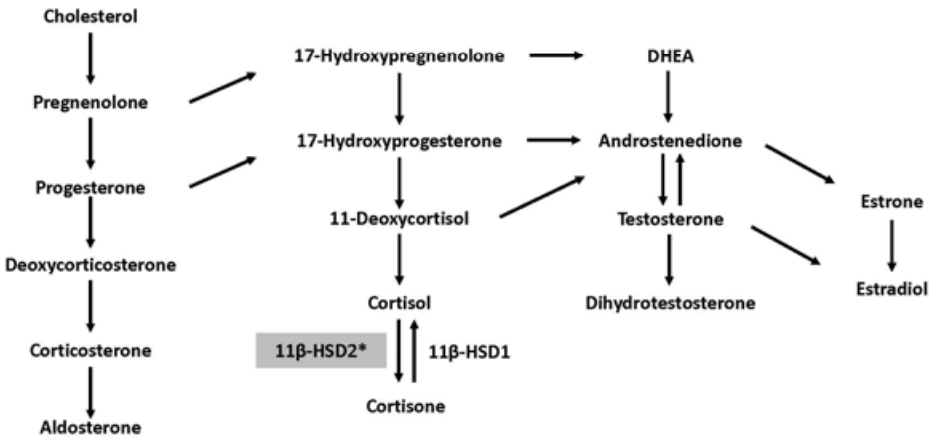
Test Name	Itraconazole 300 mg twice daily	1 month after change to voriconazole	Normal range
Aldosterone (ng/dL)	**1 (L)**	4	3 - 16
Renin activity (ng/mL/hr)	**0.13 (L)**	0.69	0.25 – 5.82
11-deoxycortisol (ng/dL)	**55 (H)**		≤42
Cortisol (mcg/dL)	11.2	13.5	4 – 22
Estradiol (pg/mL)	**40 (H)**	26	≤39
Deoxycorticosterone (ng/dL)	<16		≤15
Itraconazole (mcg/mL)	2.18		
Hydoxy-itraconazole (mcg/mL)	3.75		

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Figure 1. Itraconazole induced inhibition of 11β-HSD2 results in a build-up of precursor hormones causing the apparent mineralocorticoid excess syndrome.



11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2

***Blockade of this enzymatic step produces anincrease in precursor hormones (11-deoxycortisol), alters the cortisol:cortisone ratio, and causes a compensatory shift in enzymatic synthesis with resultant increased estradiol. The mineralocorticoid effects of increased 11-deoxycortisol produces a decrease in renin and aldosterone production.**

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