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Exceptional Case

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# Posaconazole-induced hypertension and hypokalemia due to inhibition of the 11β-hydroxylase enzyme

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## Abstract

Posaconazole is an antifungal therapy reported to cause incident hypertension. Hypokalemia is also a known side effect. The combination of hypertension and hypokalemia suggests mineralocorticoid excess. We present the case of a 15-year-old adolescent male with hypertensive urgency while on prophylactic posaconazole therapy for a combined immunodeficiency. We identify the mechanism of posaconazole-induced hypertension to be inhibition of the 11β-hydroxylase enzyme, resulting in elevated levels of the mineralocorticoid receptor activator deoxycorticosterone. Loss of function of the 11β-hydroxylase enzyme is responsible for a rare form of congenital adrenal hyperplasia and can be associated with life-threatening adrenal crisis.

**Key words:** adrenal hyperplasia, 11β-hydroxylase, hypertension, hypokalemia, mineralocorticoid excess, posaconazole

## Introduction and case report

A 15-year-old male adolescent presented to the hospital with hypertensive urgency (systolic readings up to 160 mmHg) and hypokalemia [serum potassium 2.8 mmol/L (normal 3.3–4.9)]. Due to combined immunodeficiency with hypogammaglobulinemia, he was on posaconazole therapy for fungal prophylaxis. He was admitted to the general pediatric ward for further evaluation and management. His blood pressure rose to >200 mmHg systolic and was associated with flushing and headache. He was transferred to the intensive care unit for management with intravenous antihypertensive infusions of nicardipine and esmolol to control blood pressure.

Evaluation for the cause of hypertension included an echocardiogram, magnetic resonance imaging of the brain, abdominal ultrasound with Doppler wave analysis, computerized axial tomography of the abdomen, serum aldosterone and renin levels, serum chromogranin A and urine 5-hydroxyindoleacetic acid levels for carcinoid syndrome, as well as thyroid studies. All the above studies were normal. Plasma renin and aldosterone levels were low/suppressed (renin 1.2 ng/mL/h, aldosterone <0.4 ng/dL), supporting a hyporeninemic hypertension.

Evaluation for pheochromocytoma was performed due to severe hypertension and episodic flushing. Plasma and urine metanephrines were elevated: normetanephrine 2.7 nmol/L (normal <0.9) and 1372 μg/24 h (normal <456), respectively. Plasma and urine catecholamines were also elevated three times above the reference range. Because of the elevated metanephrines and catecholamines, he underwent positron emission tomography (PET) nuclear imaging with DOTATATE peptide, which failed to show a somatostatin receptor 2 expressing paraganglioma or

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**Table 1.** Hormone, electrolyte levels and blood pressure during and after posaconazole therapy

| Test | POSA | POSA off | Normal/therapeutic range |
|---|---|---|---|
| Deoxycorticosterone (ng/mL) | 247 | 24 | 2–19 |
| 11-Deoxycortisol (ng/dL) | 2445 | 167 | 12–158 |
| Androstenedione (ng/dL) | 194 | 75 | 33–192 |
| 17-Hydroxyprogesterone (ng/dL) | 452 | 215 | 24–175 |
| Cortisol (mcg/dL) | 13 | 17 | 3–21 |
| Serum potassium (mmol/L) | 2.8 | 4.3 | 3.5–4.9 |
| Plasma renin (ng/mL/h) | 1.2 | NA | 1.2–2.4 |
| Plasma aldosterone (ng/dL) | <0.4 | NA | <21 |
| Plasma normetanephrine (nmol/L) | 2.7 | 0.28 | <0.9 |
| Posaconazole (ng/dL)[a] | 3000 | NA | >700 |
| Blood pressure (mmHg)[b] | 176/72 | 102/64 | <130/80 |

[a]Average of three levels.
[b]Average of 1 week of measurements.
NA, not available.

pheochromocytoma, ruling out the diagnosis. With the DOTATATE PET not identifying a normetanephrine-secreting tumor, it was concluded that the elevated levels of metanephrine, normetanephrine and catecholamines were elevated due to interference with the assay from esmolol and nicardipine [1].

The possibility of congenital adrenal hyperplasia (CAH) and/or the syndrome of apparent mineralocorticoid excess (AME) was raised. A serum adrenal steroid laboratory panel was sent for analysis. The patient and family did not reveal a history of chronic licorice (glycyrrhizic acid) ingestion. Licorice inhibits the 11β-hydroxysteroid dehydrogenase type 2 isoform (11β HSD2). In a review of the literature, it was found that posaconazole inhibits the same enzyme [2]. In this patient, the results of the adrenal steroid panel showed markedly elevated deoxycorticosterone and 11-deoxycortisol levels and androgens (Table 1) suggestive of a block at the level of 11β-hydroxylase and not AME from inhibition of 11β-HSD2.

Since he had no prior history of hypertension and no family history of CAH, 11β-hydroxylase deficiency CAH seemed unlikely. In addition, he previously had an extensive genetic workup of the combined immunodeficiency including whole exome sequencing, which did not identify mutations in either the *CYP11B1* gene or the *11β-HSD2* gene. To evaluate the possibility of hypertension from 11β-hydroxylase inhibition, posaconazole was stopped. Within 3 weeks of stopping, blood pressure and serum potassium normalized. A repeat adrenal steroid panel off posaconazole showed normal levels of deoxycorticosterone, 11-deoxycortisol and plasma metanephrines (Table 1).

## Discussion

This is the first case demonstrating that the mechanism of posaconazole-induced hypertension is inhibition of the 11β-hydroxylase enzyme. Previous cases of posaconazole-induced hypertension have been hypothesized to be a form of acquired AME due to 11β-HSD2 inhibition [3]. However, the testing in this patient shows a defect upstream in the adrenal steroidogenesis pathway resulting in elevated deoxycorticosterone and 11-deoxycortisol (Table 1). The supraphysiologic level of deoxycorticosterone activates the mineralocorticoid receptor. This results in excessive activity of the epithelial sodium channel in the distal tubule and collecting duct causing hypertension due to sodium and water retention as well as hypokalemia.

Posaconazole is an antifungal agent that acts by inhibiting fungal cell membrane synthesis by blocking steroidogenesis and depletion of ergosterol in the cell membrane. Adrenal steroid biosynthesis from cholesterol to aldosterone and cortisol is mediated by multiple cytochrome P450 (CYP450) enzymes that include 11β-hydroxylase. Posaconazole has not previously been reported to specifically inhibit the 11β-hydroxylase enzyme, but it is an inhibitor of the CYP450 3A4 enzyme [4]. A similar antifungal compound, ketoconazole, has a reported 98% inhibition rate of the 11β-hydroxylase enzyme at a concentration of 1 μmol/L [5].

In light of animal studies showing that posaconazole stimulates adrenal cells with an increased incidence of pheochromocytomas [4], our conclusion that metanephrine levels were elevated because of interference with the assay is questionable. Acetaminophen, amoxicillin and sulfa-based drugs are known to interfere with the assays, and he was on trimethoprim with sulfamethoxazole [1, 6]. Beta-adrenergic blockers (esmolol) and calcium channel blockers (nicardipine) increase levels of metanephrines and catecholamines, respectively [1]. Posaconazole likely induced adrenal hyperplasia (which would not be identified by PET imaging), with increased metanephrine and catecholamine levels further compounding hypertension. The return of normal plasma metanephrine levels after stopping posaconazole supports this premise (Table 1).

In conclusion, clinical studies of posaconazole therapy have reported hypokalemia in up to 30% and incident hypertension in 18% of patients [7]. Evaluation of our pediatric patient for secondary hypertension and hypokalemia implicated posaconazole as a cause of mineralocorticoid excess due to 11β-hydroxylase enzyme inhibition with adrenal hyperplasia. We suggest that those receiving posaconazole therapy be closely monitored for adverse effects. All patients on posaconazole therapy should have screening for hypertension and hypokalemia and, if detected, should undergo further endocrine evaluation accordingly.

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## Authors' contributions

K.B. and T.K.D. wrote the first draft of the manuscript. N.W., B.M. and A.E. provided critical revisions to the manuscript.

## Conflict of interest statement

None declared.

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