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In Vivo 11β-Hydroxysteroid Dehydrogenase Inhibition in Posaconazole-Induced Hypertension and Hypokalemia

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ABSTRACT We describe a case of apparent mineralocorticoid excess (AME) secondary to posaconazole therapy and suggest the biochemical mechanism. Clinical and laboratory investigation confirmed 11β-hydroxysteroid dehydrogenase inhibition and withholding therapy led to a resolution of all clinical and laboratory abnormalities. Posaconazole was later restarted at a lower dose and prevented recurrence of this syndrome. Additional studies are necessary to determine the frequency of posaconazole-induced AME and whether other azole antifungals can be associated with this phenomenon.

KEYWORDS antifungal, posaconazole, side effects

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Posaconazole is a triazole antifungal agent with a broad spectrum of antifungal activity. Frequently used for the prevention of fungal infections in high-risk populations, this agent is also useful during the treatment of multiple forms of aspergillosis (1). Recent studies have shown that the new posaconazole delayed-release tablets have superior bioavailability compared to the liquid suspension formulation (2, 3). As higher serum posaconazole concentrations have been associated with improved clinical responses (4), this formulation has been a welcome addition to available treatment options. However, higher serum and tissue levels are likely to reveal previously undescribed toxicity as adverse events attributed to "off-target" effects are observed.

We present here a 67-year-old man with chronic cavitary aspergillosis of the left lung and no history of hypertension. At the time of initial evaluation he was afebrile with a blood pressure of 114/66 mm Hg. The patient had previously received voriconazole (more than 1 year earlier) with the complaint of visual hallucinations. He had also previously received isavuconazole with frequent serum blood levels noted >10 μg/ml despite standard dosing. He refused to take either medication again and had been off antifungal therapy for 6 weeks prior to the initial evaluation. His intake laboratory values, including basic chemistries and liver tests, were within normal limits (potassium 4.1 mmol/liter). Posaconazole tablets were started (300 mg twice daily on day 1, followed by 300 mg daily). The patient tolerated the medication without complaint; however, on his return visit 35 days later, his blood pressure was noted to be 165/89 mm Hg. All other vital signs were within normal limits. A review of his laboratory values (Quest Diagnostics) revealed a potassium level of 3.4 mmol/liter and a serum posaconazole level of 4.36 μg/ml. Additional work-up was initiated and found complete suppression of renin and aldosterone, with increased 11-deoxycortisol and estradiol levels

TABLE 1 Patient's laboratory values after different doses of posaconazole[a]

Test name	Posaconazole, 300 mg daily	21 days after posaconazole cessation	Posaconazole, 100 mg daily	Normal range
ACTH (pg/ml)	47			6–50
Pregnenolone (ng/dl)	89			13–208
17-Hydroxypregnenolone (ng/dl)	147			≤905
Progesterone (ng/ml)	<0.5			<1.4
17-Hydroxyprogesterone (ng/dl)	129			37–129
Aldosterone (ng/dl)	<1 ng/dl	4	3	3–16
Renin activity (ng/ml/h)	0.11	1.34	2.47	0.25–5.82
DHEA (ng/dl)	175			61–1636
11-Deoxycortisol (ng/dl)	177	36	<20	≤42
Deoxycorticosterone (ng/dl)	2			≤15
Corticosterone (ng/dl)	885			59–1,293
Cortisol (μg/dl)	14.6			4–22
Cortisone (μg/dl)	1.4			1.2–3.5
Testosterone (ng/dl)	911			250–1,100
Free testosterone (pg/ml)	36.9			35–155
Estrone (pg/ml)	55	23		≤68
Estradiol (pg/ml)	48	35	26	≤39
Estriol (ng/ml)	<0.10	<0.10	<0.10	<0.18
Serum potassium (mmol/L)	3.4	4.9	4.4	3.5–5.3
Serum osmolality (mOsm/kg)	287		284	278–305
Urine potassium (mmol/L)	29		47	12–129
Urine osmolality (mOsm/kg)	358		557	50–1,200
Serum posaconazole (μg/ml)	4.36	NA[b]	1.24	>0.70

[a]All blood samples for laboratory testing were drawn at 8 a.m.
[b]NA, not applicable.

(Table 1). A markedly elevated cortisol/cortisone ratio (10.4) and a transtubular potassium gradient (TTKG) of 6.84 (during hypokalemia it should be less than 3) were also observed. On discussion with the patient it was decided to withhold antifungal therapy and repeat laboratory testing. Twenty-one days following cessation of posaconazole therapy his blood pressure returned to normal, and laboratory values normalized. The patient subsequently was restarted on a lower dose of posaconazole tablets (100 mg daily) in an attempt to avoid endocrinopathy. After 4 weeks of posaconazole the patient was again seen and noted to have normal blood pressure (115/63 mm Hg); his serum posaconazole level was 1.24 μg/ml, and his renin, aldosterone, 11-deoxycortisol, and estradiol levels remained at normal levels.

Posaconazole-induced disruption of the steroid biosynthesis pathway in a patient has not previously been described but has been suggested by *in vitro* studies (5). Our patient's laboratory results show clinically significant inhibition of 11β-hydroxysteroid dehydrogenase enzyme type 2 isoform (11β-HSD2) as evidenced by the elevated 11-deoxycortisol (with subsequent suppression of renin and aldosterone), the highly elevated cortisol/cortisone ratio (6, 7), and the inappropriately elevated TTKG in the setting of hypokalemia. The normal deoxycorticosterone confirms normal function of 11β– hydroxylase, and the observed effects in our patient were thus downstream from this enzyme.

The conversion of cortisol to the inactive form of cortisone is mediated by 11β-HSD2, which is the kidney isoform of 11β-HSD. Cortisone does not bind to the mineralocorticoid receptor, and thus the conversion of cortisol to cortisone is of utmost physiologic importance to reduce the quantity of cortisol and its precursor deoxycortisol (which both bind as avidly as aldosterone) available to bind the mineralocorticoid receptor (8). Plasma cortisol concentrations are approximately 100-fold higher than aldosterone concentrations, and thus without functional 11β-HSD2, cortisol acts as the primary mineralocorticoid (9). In this circumstance, even "normal" levels of cortisol can markedly increase net mineralocorticoid activity (10).

In contrast, the conversion of inactive cortisone back to cortisol is dependent upon 11β-hydroxysteroid dehydrogenase enzyme type 1 (11β-HSD1) (Fig. 1). These enzymes

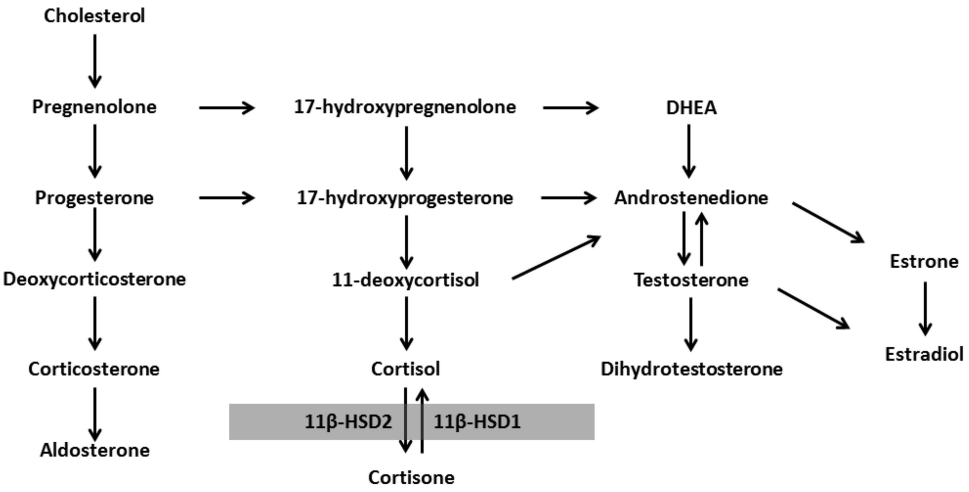

FIG 1 Inhibition of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) by posaconazole induces an increase in the precursor hormones cortisol and 11-deoxycortisol, leading to the syndrome of apparent mineralocorticoid excess. 11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; DHEA, dehydroepiandrosterone.

show relatively low overall identity (18% sequence identity between isoforms) (11). It is thus not surprising that differing affinity between these enzymes would be suggested in clinical observations. In fact, recent *in vitro* work confirmed the relative specificity of the type 2 isoform to both posaconazole and itraconazole (5). In this report, the 50% inhibitory (IC_{50}) level of posaconazole was found to be 460 $\pm$ 98 nM for 11β-HSD2 (a value exceeded by patient serum posaconazole concentrations) with little *in vitro* effect on 11β-HSD1 activity. Itraconazole and posaconazole are structurally related, and it remains unclear if inhibition of this enzyme is observed solely with these two antifungal agents or if additional investigation and subsequent reports will reveal a class effect with other triazoles in current clinical use.

Elevation in the 11-deoxycortisol level also leads to elevated 17-hydroxyprogesterone levels, which in turn feed the androgen pathway, causing excess androstenedione and testosterone. Subsequent aromatization of testosterone leads to increased estradiol levels such as those that were observed in our patient. Left unrecognized, estradiol elevation can lead to physiologic changes such as hypogonadism and gynecomastia. Prompt recognition of this syndrome in our patient likely avoided these potential side effects.

Prior studies observed hypokalemia (22%) and hypertension (11%) in patients receiving the 300-mg daily tablet formulation of posaconazole (12). In these studies, hypokalemia in those receiving posaconazole prophylaxis or treatment could be attributed to the frequency of vomiting (13%) and/or diarrhea (29%) in the hematologic malignancy population (12), where it is frequently prescribed, although it is possible that some of these patients had posaconazole-induced hypertension. Two previous reports demonstrated the association of posaconazole and hypokalemia with alkalosis, although neither provided a theoretic mechanism for these findings (13, 14). Our report demonstrates for the first time the mechanism, highlights the clinical significance, and allows for posaconazole to be added to the list of other medications/products (e.g., glycyrrhetinic acid from licorice, carbenoxolone, grapefruit juice) that lead to acquired deficiency of 11β-hydroxysteroid dehydrogenase (15, 16).

In total, these findings suggest clinically significant inhibition of 11β-HSD2 with resultant new onset hypertension and renal potassium loss attributable to posaconazole. A reduction of the posaconazole dose led to a return of the patient's blood pressure, serum potassium, and hormone indices to normal levels while still maintaining a potentially therapeutic serum drug concentration. It is unclear if specific single nucleotide polymorphisms (SNPs) in 11β-HSD2 or other genes predispose some patients to this syndrome. Screening for these side effects can likely be accomplished by

review of a patient's blood pressure and serum potassium, with further work-up dictated only by a change from pretreatment values. Future studies are needed to determine the frequency of this syndrome and if any association with SNPs exists with posaconazole-induced AME.

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