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Posaconazole-Induced Apparent Mineralocorticoid Excess

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INTRODUCTION

Posaconazole is an extended-spectrum triazole antifungal used quite frequently in the treatment of invasive fungal infections and for prophylaxis against such fungal infections in special populations like those with hematologic malignancies and neutropenia.[1] We demonstrate a state of apparent mineralocorticoid excess (AME) induced by posaconazole and consequent hypokalemia, metabolic alkalosis, and hypertension in a patient with acute myeloid leukemia.

CASE PRESENTATION

A 68-year-old Sudanese woman with a past medical history of hypertension and relapsed hepatitis B infection was admitted for management of relapsed acute myeloid leukemia (AML-M2). Over the nearly 2-month-long admission, she had been treated at various time points with cytarabine, etoposide, hydroxyurea, mitoxantrone, and lenalidomide. She had developed neutropenic sepsis secondary to multidrug-resistant *Escherichia coli* bacteremia, thigh myositis, and diarrhea secondary to *Clostridium difficile* infection. She was treated with ceftazidime and avibactum and oral vancomycin, following which her symptoms abated. She was also receiving prophylactic antimicrobials including acyclovir 400 mg twice daily and posaconazole 300 mg daily in the setting of neutropenia and tenofovir disoproxil for treatment of hepatitis B infection. She was maintained on her outpatient antihypertensive regimen of losartan 100 mg daily and metoprolol succinate 100 mg daily. Her systolic blood pressure, which had been about 120 to 130 mm Hg on admission, was noted to be raised to about 160 to 170 mm Hg despite being on the same dose of antihypertensives. Physical examination revealed moderate pallor and trace bilateral lower extremity edema.

About 3 weeks into her admission, she was found to be hypokalemic (potassium levels as low as 2.6 mEq/L), which persisted despite receiving large doses of intravenous and oral potassium supplements. She also developed alkalosis, with bicarbonate levels having increased from an admission value of 27 mEq/L to a peak value of 39 mEq/L and a venous pH of 7.52 (Table 1). Renal function was normal, and she had pancytopenia. Urine studies revealed potassium wasting with a random urine potassium/creatinine of 151 mEq/mg. Laboratory data are presented in Table 1.

The triad of hypokalemia, metabolic alkalosis, and worsening hypertension led us to suspect a hypermineralocorticoid state. Investigations targeted toward determination of the cause of this hypermineralocorticoid state revealed the following. A computed tomography of the abdomen and pelvis ruled out adrenal tumors. A normal 24-hour urine-free cortisol (UFF) made Cushing's syndrome unlikely. Serum aldosterone level and plasma renin activity were suppressed, which led us to suspect a state of AME. This was confirmed with low 24-hour urine-free cortisone (UFE) and a UFF/UFE ratio of 0.89 (normal, 0.4–0.5).

OUTCOME

Spironolactone was started, and the dose was escalated to 100 mg a day with resolution of electrolyte abnormalities. Posaconazole was discontinued after neutropenia resolved, and neither hypokalemia nor metabolic alkalosis recurred after discontinuation of spironolactone.

DISCUSSION

Hypokalemia could have been attributed to many potential etiologic factors in this patient. Gastrointestinal loss in the setting of diarrhea could certainly have

Table 1. Laboratory values

Test	Results
Hemoglobin, g/dl	7
White blood cells, per μl	1200
Platelets, $\times 10^3$/μl	17
Sodium, mEq/l	140
Potassium, mEq/l	2.6
Chloride, mEq/l	93
Bicarbonate, mEq/l	35
Blood urea nitrogen, mg/dl	11
Creatinine, mg/dl	0.8
Calcium, mg/dl	8.4
Inorganic phosphorus, mg/dl	3.0
Magnesium, mg/dl	1.6
Albumin, g/dl	2.1
Venous blood pH	7.52
Venous blood P_{CO_2}, mm Hg	46
Aldosterone, ng/dl	2 (normal, 3–16)
Plasma renin activity, ng/ml/h	0.05 (normal, 0.25–5.82)
Random urine: Na, mEq/l	117
Random urine: K, mEq/l	50
Random urine: creatinine, mg/dl	33
Random urine: chloride, mEq/l	149
Random urine: osmolality, mOsm/kg	415
24-Hour urine volume	2025 ml
24-Hour urine-free cortisol, μg	13 (normal, 4–50)
24-Hour urine-free cortisone, μg	14.6 (normal, 23–195)
Urine-free cortisol–to–urine-free cortisone ratio	0.89 (normal, 0.4–0.5)

contributed but was unlikely to be the primary cause given resolution of diarrhea well before the development of hypokalemia. Furthermore, a high urinary potassium concentration indicated renal potassium wasting. Tenofovir can cause proximal tubular dysfunction and consequent renal potassium losses, but this is usually associated with mild metabolic acidosis, not metabolic alkalosis. Longstanding hypokalemia can worsen metabolic alkalosis; however, in this patient hypokalemia preceded metabolic alkalosis only by a day.

The combination of hypokalemia, severe metabolic alkalosis, and worsening hypertension led us to suspect a state of real or AME. The 24-hour urine cortisol level was normal, which ruled out Cushing's syndrome and ectopic adrenocorticotropic hormone secretion. Low aldosterone level and low plasma renin activity indicated appropriate suppression of the renin-angiotensin-aldosterone system and explains the relative resistance of the patient's hypertension control to angiotensin receptor blocker administration. A high 24-hour UFF/UFE ratio indicated inhibition of renal 11β-hydroxysteroid dehydrogenase isoform 2 (11-βHSD2) leading to AME.[2]

Aldosterone acts on the mineralocorticoid receptor (MR), resulting in increased activity and number of epithelial sodium channels and increased activity of the basolateral Na-K ATPase channels. Given the high level of sequence identity with glucocorticoid receptor, cortisol has identical binding affinity to this receptor as aldosterone.[3,4] To prevent cortisol, with a plasma concentration 100-fold higher than aldosterone, from constitutively activating the MR even under "normal" cortisol levels, mineralocorticoid target cells, including cortical collecting cells, express the enzyme 11-βHSD2. 11-βHSD2 converts cortisol to cortisone, which is a poor agonist at the MR, thus preventing the action of cortisol on this receptor[3,4] and allowing cells to respond to much lower concentrations of aldosterone (Figure 1). The conversion of cortisol to cortisone is reflected in a low UFF/UFE ratio (i.e., 0.4–0.5).[2]

Inhibition of 11-βHSD2 can cause unrestrained stimulation of MR (Figure 2) by cortisol leading to a syndrome of AME. Inherited forms of the disease[2] are associated with very low activity of the enzyme and a very high UFF/UFE ratio (i.e., 5–20). Acquired AME caused by glycyrrhetinic acid in licorice and by carbenoxolone is associated with only partial inhibition of 11-βHSD2, and hence UFF/UFE ratios are not very high. Mild elevation of the UFF/UFE ratio in our patient (0.89) was indicative of acquired inhibition of 11-βHSD2.

Studies on patients taking posaconazole 300 mg for prophylaxis observed hypertension in 11% and hypokalemia in 22%.[5] Hypokalemia was attributed to vomiting and diarrhea in some, especially in the setting of a hematologic malignancy. Thompson *et al.*[6] demonstrated clinically significant inhibition of 11-βHSD2 as the cause of AME induced by posaconazole. They also demonstrated resolution of dyselectrolytemia after cessation of posaconazole and lack of recurrence with a lower dose of posaconazole (100 mg daily). In vitro studies by Beck *et al.*[7] demonstrated inhibition of 11-βHSD2 by posaconazole (moderate) and itraconazole (more potent), with little effect on the type 1 isoform. They attributed this relatively specific inhibition of 11-βHSD2 to the relatively large azole scaffold size in the structurally related posaconazole and itraconazole.

Beck *et al.*[7] also reported the 50% inhibitory concentration of posaconazole for 11-βHSD2 as 460 ± 98 nM. This is lower than the recommended posaconazole trough level of >700 ng/mL for prophylaxis and >1000 to 1250 ng/ml for treatment of fungal infections,[8] indicating potential for inhibition of this enzyme even at usual clinical doses. However, not every individual who gets posaconazole develops dyselectrolytemia, and this raises the possibility of a genetic predisposition for this syndrome.

Hypokalemia and hypertension have been reported with the use of itraconazole[9] but not with other azole

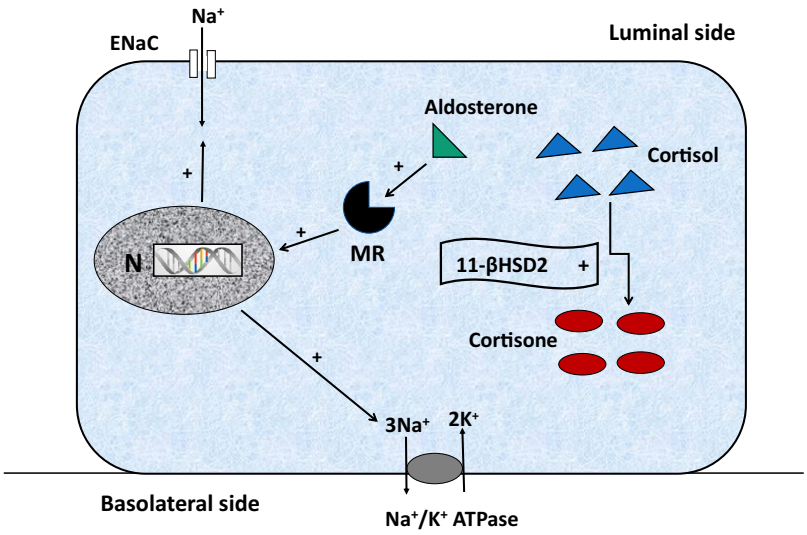

Figure 1. Under normal circumstances aldosterone exerts its effect on the principal cells in the distal tubule and cortical collecting duct by binding to a cytoplasmic mineralocorticoid receptor (the receptor is translocated to the nucleus after binding to aldosterone). The effects are increased activity and number of epithelial sodium channels (ENaC) and increased activity of the basolateral Na-K ATPase channels. Cortisol is converted to cortisone by the action of 11β-hydroxysteroid dehydrogenase 2 (11-βHSD2), thereby preventing action on the mineralocorticoid receptor (MR). N, nucleus.

antifungals. In a recent study, Beck *et al.*[S1] demonstrated lack of 11-βHSD2 inhibition by fluconazole, isavuconazole, and voriconazole.

Boughton *et al.*[S2] also detected elevated levels of 11-deoxycorticosterone (11-DOC) and 11-deoxycortisol, which they attributed to inhibition of 11β-hydroxylase (CYP11B1), akin to the inherited condition congenital adrenal hyperplasia. Beck *et al.*[S1] demonstrated potent inhibition of CYP11B1 by posaconazole, moderate inhibition by itraconazole, and very weak inhibition by voriconazole, fluconazole, and isavuconazole. CYP11B1 is an enzyme that is stimulated by adrenocorticotropic hormone and catalyzes conversion of 11-DOC to corticosterone and 11-deoxycortisol to cortisol. 11-DOC and 11-deoxycortisol have moderate activity at the MR, and a buildup of these metabolic intermediates caused by inhibition of CYP11B1 can lead to excessive activation of the MR. This would make the condition potentially responsive to adrenocorticotropic hormone suppression by exogenously administered glucocorticoids. We did not check the serum steroid profile for this patient; however, it is likely that the hypertension and

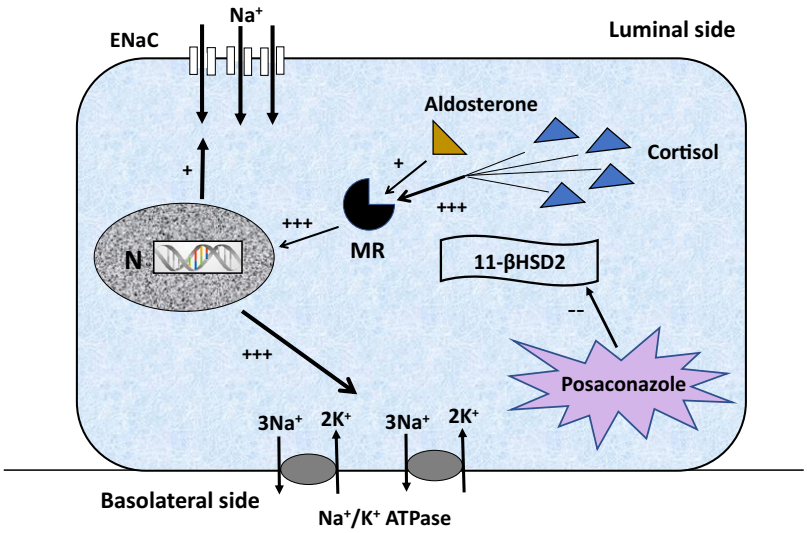

Figure 2. Posaconazole inhibits 11β-hydroxysteroid dehydrogenase 2 (11-βHSD2), and cortisol is now available to bind to the mineralocorticoid receptor (MR). Because there is more cortisol than aldosterone, there is amplification of MR action causing increase in activity and number of epithelial sodium channels (ENaC) and Na-K ATPase channels. Excess uptake of sodium leads to hypertension and creates increased electronegativity causing K^+ and H^+ losses and leading to hypokalemia and alkalosis (not shown in this figure). N, nucleus.

Table 2. Teaching points

1.	Posaconazole is being increasingly used for treatment and prophylaxis against invasive fungal infections.
2.	Posaconazole (and itraconazole) can cause inhibition of 11β-hydroxysteroid dehydrogenase 2 in the principal cells and induce a state of apparent mineralocorticoid excess leading to hypokalemia, metabolic alkalosis, and new-onset or worsening of chronic hypertension.
3.	Posaconazole and itraconazole can also cause inhibition of CYP11B1 (11β-hydroxylase) leading to accumulation of 11-deoxycorticosterone and 11-deoxycortisol, which have moderate agonist action on the mineralocorticoid receptor and can contribute to the hypertension and dyselectrolytemias.
4.	Patients on posaconazole should be monitored for hypokalemia, hypertension, and metabolic alkalosis.
5.	Management of such individuals includes either cessation of posaconazole (if feasible, and switching to another antifungal), decreasing the dose of posaconazole, or initiation of a mineralocorticoid receptor antagonist like spironolactone or eplerenone.

dyselectrolytemias were caused by accumulation of 11-DOC and 11-deoxycortisol in addition to inhibition of 11-βHSD2.

AME induced by posaconazole can be treated with an aldosterone receptor antagonist (i.e., either spironolactone or eplerenone) or with the epithelial sodium channel blockers amiloride or triamterene. However, MR antagonists have the theoretical advantage over epithelial sodium channel inhibitors of inhibiting epithelial sodium channel–independent aldosterone actions.

In conclusion, we demonstrated clinically significant inhibition of 11-βHSD2 by posaconazole resulting in hypokalemia, metabolic alkalosis, and hypertension. Individuals taking posaconazole should be monitored for these dyselectrolytemias on a regular basis. Treatment requires either cessation of posaconazole, dose reduction, or the use of an MR antagonist (spironolactone, eplerenone) (Table 2).

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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