

PRIMARY ADRENAL INSUFFICIENCY SECONDARY TO CHRONIC POSACONAZOLE USE

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ABSTRACT

Objective: Posaconazole (PSO) is commonly used in the treatment of invasive fungal infections. PSO-induced primary adrenal insufficiency (PAI) is rare, and we present what we think to be the third case report of its incidence. We want to bring awareness to this rare but significant side effect that can impact management and monitoring of patients on this medication.

Methods: After clinical assessment, the patient was evaluated with diagnostic studies including measurements of cortisol, adrenocorticotropic hormone, renin activity, and aldosterone levels. Imaging studies such as abdominal computed tomography were also performed.

Results: A 65-year-old man with a history of hemophagocytic lymphohistiocytosis on a dexamethasone taper, complicated with mucormycosis on PSO presented to the emergency department with weakness, fatigue, decreased appetite, orthostatic hypotension, low morning cortisol (0.4 µg/dL), low adrenocorticotropic hormone (3.4 pg/mL), elevated plasma renin (16.7 ng/mL/hour), and low-normal aldosterone (1.7 ng/dL). Abdominal computed tomogra-

phy imaging revealed bilaterally intact adrenal glands. A diagnosis of PSO-induced PAI was made. Fludrocortisone was initiated in addition to glucocorticoids with improvement of fatigue, appetite, blood pressure, and normalization of sodium and potassium. A month after discontinuing PSO, steroids and fludrocortisone were discontinued with measured morning cortisol of 13 µg/dL and an adrenocorticotropic hormone level of 53.9 pg/mL, both normal.

Conclusion: Available data suggest that the adverse effect profile of PSO is more favorable than other triazoles. However, our case is the third report suggesting that PAI may be an underrecognized side effect. Awareness of this complication is particularly important in patients with severe or resistant fungal infections. (AACE Clinical Case Rep. 2020;6:e62-e64)

Abbreviations:

ACTH = adrenocorticotropic hormone; PAI = primary adrenal insufficiency; PSO = posaconazole; SAI = secondary adrenal insufficiency

INTRODUCTION

Primary adrenal insufficiency (PAI) is a rare, life-threatening condition characterized by impaired secretion of adrenal glucocorticoids and mineralocorticoids. Its prevalence in Europe is estimated at 82 to 144 cases per million (1-3). It is estimated that from the entire U.S. population the number of affected individuals could be 55,000 to 100,000 individuals (4).

Symptoms and signs of PAI depend on the acuity and degree of adrenal function loss (2). Usually clinical features are nonspecific and include weakness, anorexia, depression, anxiety, weight loss, and abdominal pain (1,2). Orthostatic hypotension, salt craving, and hyperkalemia are more specifically related to mineralocorticoid deficiency

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cy (2,5). In PAI, patients typically will have a compromised adrenal cortex with inadequate cortisol secretion which leads to reduce feedback to the hypothalamic-pituitary axis and increased adrenocorticotropic hormone (ACTH) levels (2,5).

Compared with secondary adrenal insufficiency (SAI), PAI is particularly marked by the disruption of the adrenal mineralocorticoid system (5). Low aldosterone levels translate into potassium accumulation, salt wasting, and hypovolemia which stimulate renin production (6,7).

Treatment of invasive and refractory fungal infections continues to be a challenge; posaconazole (PSO) is a relatively new member of the azole antifungal family and its use, especially high doses, has increased in patients with hematologic malignancies and immunocompromised patients with invasive resistance disease (8,9). PSO-induced PAI is a rare entity; only 2 cases have been previously described in the literature (10-12). In the present manuscript we describe a third case of PSO-induced PAI.

CASE REPORT

A 65-year-old man with a medical history of mixed connective tissue disease and sclerosing colitis was hospitalized due to respiratory, liver, and kidney failure. He was later diagnosed with hemophagocytic lymphohistiocytosis. The patient was treated using the hemophagocytic lymphohistiocytosis-94 protocol, which includes 8 weeks of high-dose pulse dexamethasone. In addition, during this period, he was also found to have invasive mucormycosis, which was initially treated with amphotericin and PSO. Once fungal culture sensitivities were available, amphotericin was discontinued and he was started on PSO at 500 mg daily.

The patient was discharged on dexamethasone at 2 mg daily and was instructed to taper the steroid dose by 0.5 mg/week to prevent SAI after prolonged high-dose steroid use. While taking 1 mg of dexamethasone, he developed weakness, decreased appetite, and became lethargic. The dexamethasone dose was increased to 3 mg daily by his oncologist and PSO and chemotherapy were continued.

Due to worsening fatigue and deterioration of the patient's condition, he was brought to the emergency department at our institution. Upon arrival, he was noted to have persistent orthostatic hypotension despite intravenous fluids, as well as a serum sodium of 130 mmol/L and potassium of 5.1 mmol/L, which raised the possibility of mineralocorticoid deficiency.

Further endocrinologic investigation, while the patient was on dexamethasone, revealed a suppressed cortisol level of 0.4 mg/dL (reference range is 10.0 to 20.0 µg/dL), suppressed ACTH at 3.4 pg/mL (reference range is 7.2 to 63.3 pg/mL), elevated plasma renin activity of 16.700 ng/mL/hour (reference range is 0.167 to 5.380 ng/mL/hour),

and inappropriate low-normal aldosterone level of 1.6 ng/dL (reference range is 0.0 to 30.0 ng/dL). The laboratory findings were suggestive of suppressed pituitary axis with concomitant primary mineralocorticoid deficiency, which raised the concern for intrinsic adrenal dysfunction due to PSO. Abdominal computed tomography imaging revealed bilaterally intact adrenal glands. Fludrocortisone (100 µg twice daily) was started in addition to the dexamethasone. The patient eventually displayed significant improvement in symptoms with normalization of electrolytes and blood pressure. Dexamethasone was eventually switched to hydrocortisone to achieve the lowest physiologic glucocorticoid dose possible and avoid iatrogenic Cushing syndrome.

After a total of 6 months on PSO, the patient was switched to isavuconazole and a month later hydrocortisone and fludrocortisone were discontinued. Repeated morning cortisol was found to be 13 µg/dL (reference range is 10 to 20 µg/dL) with an appropriate ACTH of 53.9 pg/mL (reference range is 7.2 to 63.3 pg/mL), and the patient remained adrenal sufficient.

DISCUSSION

This is a case report about a patient who presented with initial symptoms of fatigue, refractory orthostatic hypotension, hyponatremia, and hyperkalemia after prolonged use of PSO. Although symptoms initially raised the concern of possible SAI induced by high-dose glucocorticoids, laboratory findings (hyponatremia, hyperkalemia, high renin, low aldosterone) and clinical findings (hypotension) were suggestive of mineralocorticoid deficiency. In the setting of PSO-induced adrenal mineralocorticoid deficiency associated with cortisol deficiency, which is likely due to intrinsic adrenal disease, this combination is supportive of a diagnosis of PSO-induced PAI. In addition, improvement of symptoms was observed after starting fludrocortisone and continuation of physiologic glucocorticoid dose.

PAI induced by PSO has been mentioned in phase III clinical trials in patients treated for more than 6 months (8). It is interesting to note that the patients only received the medication for 3 months or less (10,11). One case was a 44-year-old woman with type 1 diabetes mellitus who developed mucormycosis similar to our patient and was treated with 300 mg of PSO for over 2 months. She presented with hypoglycemia and hypotension; inadequate adrenal response was confirmed by a low-dose ACTH stimulation test (11).

The second case was a 63-year-old man with type 2 diabetes mellitus and chronic myelomonocytic leukemia receiving chemotherapy. He was also receiving antifungal prophylaxis with PSO at 300 mg daily for 3 months before developing fatigue, poor appetite, nausea, and emesis. After confirming PAI with a conventional-dose ACTH stimulation test, he was started on fludrocortisone

and hydrocortisone; it is mentioned that the only steroid exposure this particular patient had was an intraspinal injection a month prior to starting PSO (10). These patients were different from ours in that they were not treated with steroids for a prolonged period of time prior to presentation and a primary etiology was identified earlier.

PSO is a known inhibitor of the enzyme CYP3A4, and for this reason it can potentially interact with other medications that are metabolized via the CYP3A4 enzyme system (8). The hepatic metabolism of glucocorticoids occurs via this system (12). It has been recognized that interactions between dexamethasone, which belongs to the glucocorticoid family, and triazoles may lead to increased systemic cortisol concentrations with the subsequent suppression of corticotropin-releasing hormone and ACTH secretion, which could result in SAI (12,13).

An interesting aspect of our case is the fact that our patient was previously on high-dose glucocorticoids for a prolonged period of time as part of the hemophagocytic lymphohistiocytosis-94 treatment protocol which consists of an 8-week induction regimen with etoposide and dexamethasone (14). He was using dexamethasone at the time when the labs were drawn during his visit to the emergency department which explains the suppressed ACTH and cortisol levels, but this would not explain the elevated renin and inappropriate low-normal aldosterone levels in the setting of hyperkalemia, hyponatremia, and refractory orthostatic hypotension.

Aldosterone production is controlled mainly by the renin-angiotensin-aldosterone system, and its production is not decreased in SAI (5). It is important to measure both aldosterone and renin if there is a suspicion for PAI; in some instances mineralocorticoid deficiency may predominate and be the only indication that a patient has PAI (2,5,15). Elevated plasma renin activity with a normal or low aldosterone level, as observed in the present case, would suggest PAI (2). Replacement therapy with fludrocortisone is usually effective (5,14).

Van der Pas et al (16) compared the in vitro effects on adrenocortical steroidogenesis of ketoconazole and fluconazole using primary cultures of 9 human adrenocortical tissues. They observed that by inhibiting the enzymes 11 β -hydroxylase and 17-hydroxylase, both fluconazole and ketoconazole can disrupt cortisol production. It was also noted that for this reason both drugs could induce PAI in a dose-dependent manner (16). The exact mechanism by which PSO causes PAI is unknown, but it is thought to involve steroidogenesis inhibition in a similar manner as other members of the azole family (10).

CONCLUSION

Azoles have been related to impairment of adrenal steroidogenesis, and have been identified as a cause of PAI (8,17). To the best of our knowledge, the present

study reports on the third case of PAI directly related to the chronic use of PSO. Clinicians should be aware of these rare but possible interactions. Identifying mineralocorticoid and glucocorticoid deficiencies promptly can impact the care of the patient including quality of life, hospital stay duration, and even risk of mortality (18).

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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