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Posaconazole-induced primary adrenal insufficiency concomitant with pseudoaldosteronism under normal blood pressure

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Summary

Several reports focus on azole-induced primary adrenal insufficiency (PAI); however, none have specifically focused on the absence of hypotension and hyperkalemia among the clinical features of adrenal insufficiency (AI). Here, we report a case of posaconazole-induced PAI with normal blood pressure. A 74-year-old male patient was diagnosed with lymphoma in July 2019 and underwent chemotherapy. He gradually began to experience anorexia, fatigue, and a fever of 37°C–38°C from mid-March 2022. He was diagnosed with pneumonia on April 4, 2022, and antibiotics and posaconazole at 300 mg daily were initiated post-hospitalization. Symptoms of anorexia, nausea, fatigue, and fever demonstrated no improvement despite the regression of the consolidation on the chest computed tomography. The early morning cortisol level was 2.4 μg/dL despite a high adrenocorticotropic hormone (ACTH) level (101.7 pg/mL). Therefore, we diagnosed the patient with PAI according to the low cortisol level (maximum of 8.6 μg/dL at 60 min) in a rapid ACTH stimulation test. Despite having PAI, the patient exhibited normal blood pressure and hypokalemia. Posaconazole was considered to cause PAI; therefore, it was discontinued, and hydrocortisone replacement was initiated. His symptoms improved, and rapid ACTH stimulation test reassessment 1 month after posaconazole discontinuation revealed normal basal ACTH, cortisol, and ACTH response. However, the renin–angiotensin–aldosterone system did not fully improve, as opposed to the hypothalamic–pituitary–adrenal axis. Posaconazole inhibits 11β-hydroxylase and 11β-hydroxysteroid dehydrogenase type 2, causing pseudohyperaldosteronism, which persists. Notably, posaconazole causes PAI without hypotension and hyperkalemia, which are its major clinical characteristics.

Learning points

- Posaconazole causes PAI within 1 month of initial administration.
- Posaconazole-induced PAI may not present with hypotension or hyperkalemia.
- The hypothalamic–pituitary–adrenal axis improves, but the renin–angiotensin–aldosterone system may take longer to recover, as changes persist even 1 month after posaconazole discontinuation.
- Hypokalemia treatment should continue carefully until pseudohyperaldosteronism resolution.

Keywords: adrenal; pituitary; hypothalamus; steroidogenesis

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Background

Previous reports documented azole-induced AI (1, 2, 3, 4). However, few reports make qualified AI diagnoses and hypothalamic–pituitary–adrenal (HPA) axis and renin–angiotensin–aldosterone (RAA) system reassessments after posaconazole discontinuation. Moreover, no reports focus on the major clinical features of AI, such as hypotension. We report a case of posaconazole-induced primary AI (PAI) without hypotension or hyperkalemia, diagnosed based on loading tests and with both HPA axis and RAA system reassessments 1 month after posaconazole discontinuation. A literature review on posaconazole-induced PAI featuring blood pressure and potassium levels is also provided.

Case presentation

A 74-year-old male patient was diagnosed with diffuse large B-cell lymphoma (DLBCL) in July 2019, received three chemotherapy cycles from August 2019 to January 2021, and remained in remission. Dexamethasone at 6.6 mg was administered once per cycle with all chemotherapies to prevent nausea and allergic reactions. He received fluconazole at 100 mg daily from July 2019 to February 2022 to prevent fungal infection. He gradually began experiencing anorexia, fatigue, and a fever of 37°C–38°C from mid-March 2022. He was admitted to the hospital and diagnosed with pneumonia on April 4, 2022. Post-hospital admission, antibiotics (azithromycin, levofloxacin, and tazobactam-piperacillin) and posaconazole at 300 mg daily were initiated.

The symptoms exhibited no improvement despite the regression of the consolidation on the chest computed tomography (CT). Given the patient's fatigue and anorexia, the attending physician suspected adrenal insufficiency and measured an early morning serum cortisol level 19 days after admission, which was low at 2.4 μg/dL (reference range: 6.24–18.0 μg/dL). Therefore, he was referred to the Department of Diabetes and Endocrinology for consultation. His physical assessment revealed blood pressure within normal limits at 126/75 mmHg, a heart rate of 75 beats per minute, regular body temperature of 37.8°C, and percutaneous oxygen saturation (SpO_2) of 98% while breathing room air. He presented with severe fatigue, accompanied by nausea and abdominal pain. His joints, skin, nails, or oral cavity exhibited no pigmentations. Pitting edema was observed in the lower legs; however, myalgia was not present. His medical history included DLBCL, hypertension, and hyperuricemia. His medication history included amlodipine besylate, febuxostat, and magnesium oxide. A history of regular steroid or diuretic administration for 4 weeks or longer was not reported.

Table 1 Blood tests on consultation.

Laboratory investigation	Reference range, adults	On consultation
WBC (/μL)	3,900–8,800	2,000
Neutrophils (%)	32–73	37.0
Lymphocytes (%)	18–59	36.9
Eosinophils (%)	0–6	5.9
RBC (×10⁴/μL)	380–560	266
Hb (g/dL)	13.4–17.5	9.2
Platelets (×10⁴/μL)	13.9–37.3	5.7
Alb (g/dL)	4.1–5.1	2.7
BUN (mg/dL)	8.0–20.0	25.0
Cr (mg/dL)	0.65–1.07	1.61
Na (mmol/L)	138.0–145.0	140
K (mmol/L)	3.6–4.8	3.2
Cl (mmol/L)	101.0–108.0	104
Ca (mg/dL)	8.8–10.1	7.4
Adjusted Ca		8.7
BS (mg/dL)	73–109	78
eGFR (mL/min/1.73 m²)	60-	33.5
TSH (μIU/mL)	0.50–5.00	3.300
Free T3 (pg/dL)	2.3–4.0	2.38
Free T4 (ng/dL)	0.90–1.70	1.38
Cortisol (μg/dL)	6.24–18.0	2.4
ACTH (pg/mL)	8.7–61.5	101.7
Renin activity (ng/mL/h)	0.2–2.3	0.4
Aldosterone (pg/mL)	4.0–82.1	<0.4
Adrenocortical autoantibody	Negative	Negative

WBC, white blood cells; Neutro, neutrophils; Lymph, lymphocytes; Eosino, eosinophils; RBC, red blood cells; Hb, hemoglobin; Plt, platelets; Alb, albumin; BUN, blood urea nitrogen; Cr, creatinine; Na, sodium; K, potassium; Cl, chlorine; Ca, calcium; BS, blood sugar; eGFR, estimated glomerular filtration rate; TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine; ACTH, adrenocorticotropic hormone.

Investigation

Table 1 shows the blood test results at the consultation. Pancytopenia related to DLBCL was observed. Biochemical investigation revealed renal dysfunction and hypokalemia (3.2 mmol/L; reference range: 3.6–4.8). Endocrine assessment revealed euthyroid function, high adrenocorticotropic hormone (ACTH) level (101.7 pg/mL; reference range: 8.7–61.5), low cortisol level (2.4 μg/dL), low renin activity (0.4 ng/mL/h; reference range: 0.2–2.3), and aldosterone (reference range: 4.0–82.1) was undetectable, and absence of adrenocortical autoantibodies. Infectious disease screenings were negative for beta-D-glucan and cytomegalovirus antigen. Triple sputum examinations and polymerase chain reaction eliminated tuberculosis. Plain head magnetic resonance imaging revealed no pituitary gland tumors, enlargement, or atrophy, and plain abdominal CT demonstrated no adrenal enlargement, atrophy, infarction, hematoma, or metastasis.

A rapid ACTH stimulation test was conducted. ACTH was increased at 102.7 pg/mL before loading, and cortisol exhibited a low response after 30 (7.4 μg/dL) and

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Table 2 Endocrinological investigations on consultation.

	Rapid ACTH stimulation test		
	0 min	30 min	60 min
Cortisol (μg/dL)	3.8	7.4	8.6
ACTH (pg/mL)	102.7		

60 (8.6 μg/dL) min of loading (Table 2). The patient was diagnosed with PAI based on the clinical symptoms, early morning cortisol, ACTH, and test results, and the treatment was initiated. Posaconazole was discontinued, considering the possibility that it caused PAI, and intravenous amphotericin B was initiated instead.

Treatment

Oral hydrocortisone (30 mg/day for 3 days) was initiated to improve PAI symptoms after the first ACTH stimulation test. The treatment was switched to intravenous hydrocortisone (50 mg/day for 7 days) for bronchoscopy and then decreased gradually to 25 mg/day for 4 days, followed by oral hydrocortisone (30 mg/day for 5 days). Finally, the patient was discharged on oral hydrocortisone (15 mg/day).

Outcome and follow-up

Intense fatigue and nausea improved 3 days after treatment initiation; anorexia also improved. Approximately 1 month after posaconazole discontinuation, a rapid ACTH stimulation test was conducted again, with hydrocortisone discontinued on the day of the test and a day prior. Basal ACTH and cortisol levels improved (ACTH: 19.5 pg/mL; cortisol: 9.7 μg/dL) with a normal cortisol response 30 and 60 min after loading at a maximum value of 18.9 μg/dL (Table 3). Aldosterone increased from being undetectable to 21.8 pg/mL; however, renin activity decreased from 0.4 ng/mL/h to undetectable (Table 4). The patient was discharged 4 weeks after treatment initiation. We decided to gradually taper off the hydrocortisone at our clinic because voriconazole, which is a kind of azole antifungal that is easy to administer as an oral medication, was commenced on discharge day. Pitting edema and mild lightheadedness persisted; however, myalgia was not observed after hospital discharge.

Table 3 Endocrinological investigations 1 month after discontinuation.

	Rapid ACTH stimulation test		
	0 min	30 min	60 min
Cortisol (μg/dL)	9.7	15.8	18.9
ACTH (pg/mL)	19.5		

Table 4 Renin activity and aldosterone on consultation, and 1 month after discontinuation.

	On consultation	1 month after discontinuation
Renin activity (ng/mL/h)	0.4	<0.2
Aldosterone (pg/mL)	<0.4	21.8

Hypokalemia persisted in the blood test 1 month after discharge (Table 5).

Discussion

Azoles are widely used for prophylaxis in patients at high risk of invasive fungal infection. Azole-induced AI was first reported in the 1980s with ketoconazole (1, 5). Fluconazole had been discontinued 1 month before the onset of symptoms. Although adrenal function had not been previously evaluated, fluconazole was excluded as the cause of PAI, as adrenal function recovers within approximately 10 days after discontinuation, and PAI has been reported mainly at high doses (e.g. 400 mg daily) (2). Posaconazole suppresses 11β-hydroxylase, consequently decreasing aldosterone and cortisol generation from 11-deoxycorticosterone and 11-deoxycortisol, respectively (Fig. 1) (3). Therefore, posaconazole is considered the cause of PAI.

Table 6 summarizes reports of posaconazole-induced PAI (1, 3, 4). Of three cases, two by Miller *et al.* and Araque *et al.* described a recent or current history of steroid administration. Such cases may have reduced adrenal reserve capacity based on a history of steroid administration and may be more vulnerable to posaconazole-related side effects. Furthermore, patients who have medications inducing CYP3A4, such as rifampicin, phenytoin, and barbiturate, may be

Table 5 Blood and urine tests 1 month after discharge.

Laboratory investigation	Reference range, adults	1 month after discharge
Albumin (g/dL)	4.1–5.1	3.8
BUN (mg/dL)	8.0–20.0	36.0
Cr (mg/dL)	0.65–1.07	2.08
Na (mmol/L)	138.0–145.0	145
K (mmol/L)	3.6–4.8	3.0
Cl (mmol/L)	101.0–108.0	106
eGFR (mL/min/1.73 m^2)	60-	25.3
Urinalysis		
Sodium, mmol/L	None by spot	34.7
Potassium, mmol/L	None by spot	21.39
Chlorine, mmol/L	None by spot	24.3
Creatine, mmol/L	None by spot	84

Alb, albumin; BUN, blood urea nitrogen; Cr, creatinine; Na, sodium; K, potassium; Cl, chlorine; eGFR, estimated glomerular filtration rate.

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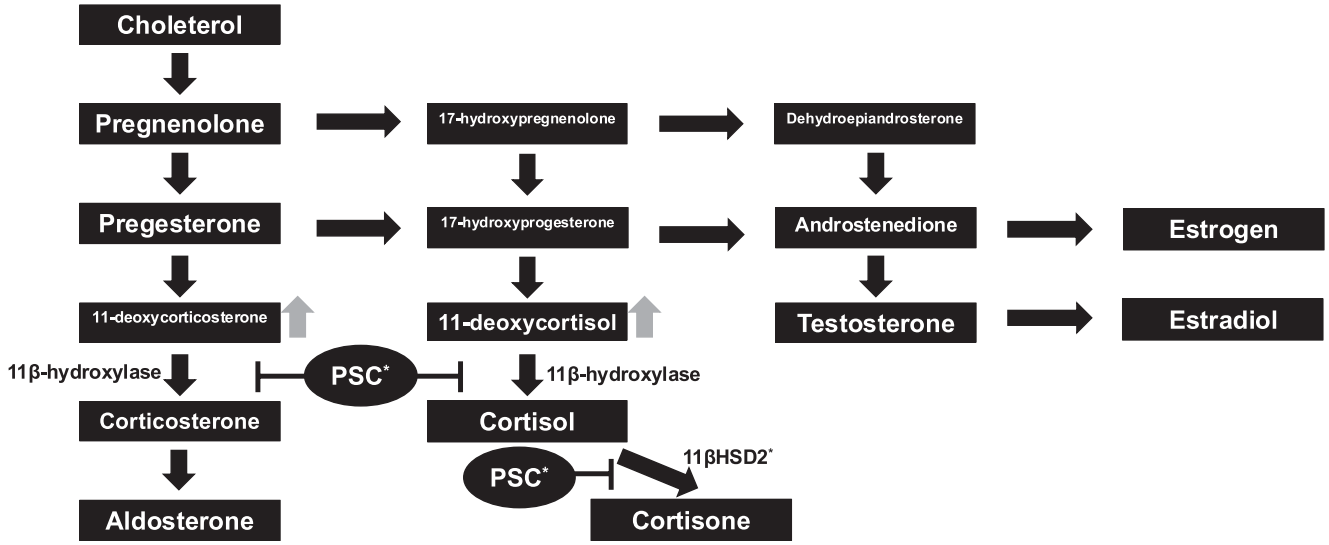

Figure 1

Adrenal steroid pathway. Abbreviations: PSC, posaconazole; 11βHSD, 11β-hydroxysteroid dehydrogenase.

vulnerable to posaconazole-related side effects due to cortisol metabolism acceleration (4, 6). Concomitant medications should be carefully reviewed.

Miller *et al.* and Villar-Prados *et al.* reported that the durations from medication usage to PAI onset were 3 and 5 months, respectively. Moreover, posaconazole-induced PAI has been mentioned in patients treated for longer than 6 months in phase III clinical trials (4). In this case, PAI developed after just 23 days of posaconazole administration, indicating that even less than 1 month of exposure can be sufficient to induce PAI.

Patients with PAI are at risk of life-threatening acute AI, with hypotension as a major clinical feature reported in more than 90% of cases. Laboratory results indicated hyperkalemia in 60–65% of patients due to mineralocorticoid deficiency (6, 7). Of the three cases listed in Table 6, two by Miller *et al.* and Villar-Prados *et al.* demonstrated blood pressure of 125/60 and 129/94 mmHg, which were within normal limits, and hypokalemia of 3.1 and 2.9 mmol/L, respectively (1, 3). Araque *et al.* revealed orthostatic hypotension and hyperkalemia of 5.1 mmol/L; however, the patient underwent endocrinological assessments under oral dexamethasone (3 mg daily). Furthermore, this implies secondary AI that may be challenging to distinguish from PAI (4).

This case demonstrated normal blood pressure (126/75 mmHg; systolic range: 120–140 mmHg during hospitalization) and hypokalemia (3.2 mmol/L), despite the presence of confounding factors such as poor oral intake and extracellular fluid administration. Three cases, including this case, demonstrated normal blood pressure and hypokalemia despite PAI. As previously mentioned posaconazole inhibits 11β-hydroxylase and is the strongest azole.

This mechanism leads to the accumulation of 11-deoxycortisol and 11-deoxycorticosterone, which, in supraphysiological amounts, can directly activate

Table 6 Case reports on primary adrenal insufficiency with posaconazole.

	Miller *et al.* (1)	Villar-Prados *et al.* (3)	Araque *et al.* (4)
Age	63	56	65
Gender	Male	Male	Male
Dose, daily	300 mg	300 mg	500 mg
Duration of medication	3 months	5 months	Unidentified
Blood pressure*, mmHg	125/60	129/92	Orthostatic hypotension (unknown value)
Potassium level* (mmol/L)	3.1	2.9	5.1
Others	5 steroid injections administered into the patient's back before admission		Evaluation under dexamethasone 3 mg/day

*Value on admission or consultation.

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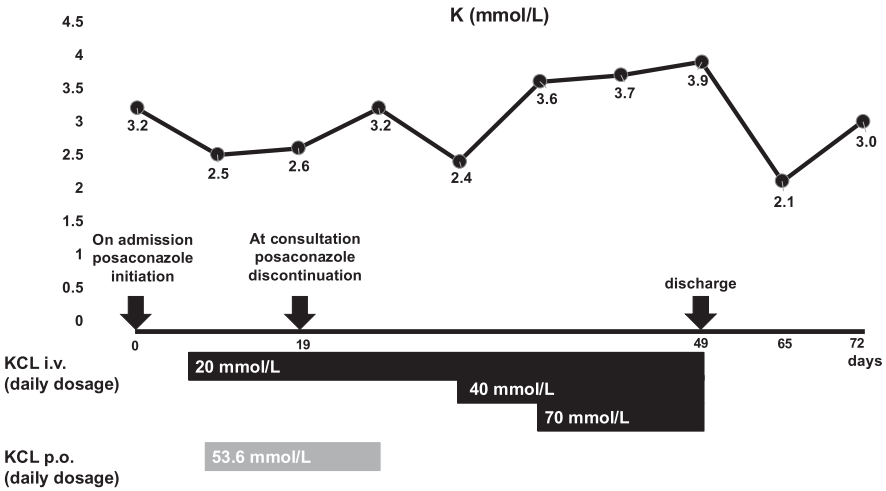

Figure 2

Trend in the serum potassium level over time and supplementation. days, days from the date of admission; K, potassium; KCL, potassium chloride; i.v., intravenous; p.o., per os.

mineralocorticoid receptors, resulting in hypertension and hypokalemia. Furthermore, posaconazole has potential 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) inhibitor activity *in vitro*, which causes pseudohyperaldosteronism (Fig. 1) (5). Consequently, posaconazole-induced PAI may not demonstrate hypotension and hyperkalemia, which are characteristics of PAI.

Approximately 1 month after discontinuation of posaconazole, adrenal function within the HPA axis had improved (Table 3); conversely, renin activity decreased from 0.4 ng/mL/h at the time of consultation to undetectable levels. However, an increased aldosterone level, from under sensitivity to 21.8 pg/mL was observed. Figure 2 illustrates the trend in potassium levels in this case. On admission, the patient had mild hypokalemia, which worsened to 2.5 mmol/L 1 week after posaconazole initiation, and potassium supplementation was started. Hypokalemia persisted despite massive supplementation and worsened after completing supplementation at discharge. Urinary potassium of 21.39 mmol/L was more than 20 mmol/L at a serum potassium level of 3.0 mmol/L, indicating renal potassium loss (Table 5). In this case, we consider that 11β-hydroxylase activity recovered, whereas that of mineralocorticoid by 11-deoxycortisol and 11-deoxycorticosterone persisted, or pseudohyperaldosteronism was induced with 11β-HSD2 inhibition and did not resolve fully 1 month after posaconazole discontinuation. The persistent clinical findings of pitting edema and mild lightheadedness support the pseudohyperaldosteronism diagnosis.

The duration of increased mineralocorticoid activity due to 11-deoxycortisol and 11-deoxycorticosterone is unknown, despite decreased urinary aldosterone 3 days after excess 11-deoxycorticosterone administration (8). In licorice-induced pseudohyperaldosteronism, serum renin activity and aldosterone levels returned to the normal range 2–4 months after licorice discontinuation (9). Davis *et al.* reported 20 posaconazole-induced pseudohyperaldosteronism cases. Regarding cases with hypokalemia and suppressed renin activity, 11-deoxycortisol levels tend to return to normal earlier than renin activity after posaconazole discontinuation or reduction (10).

Therefore, as the HPA axis recovers, careful management of hypokalemia should be continued until pseudohyperaldosteronism resolves.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work reported.

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Patient consent

Written informed consent was obtained from the daughter of the deceased patient for the publication of the clinical details.

Author contribution statement

MK wrote the first draft. The other authors supervised the first author.

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