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Case Report
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Posaconazole-Induced Uncontrolled Hypertension in Allogeneic Hematopoietic Transplant

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Abstract

Posaconazole is a triazole antifungal agent with a broad-spectrum antifungal activity; it is frequently used as prophylaxis and treatment of fungal infections. We here in document the first report of posaconazole-induced uncontrolled hypertension in an allogeneic transplant recipient, and provide a brief review of such reports in the literature. Recognition of this phenomenon led to a dramatic decrease in the number and dose of antihypertensive medications needed, and facilitated optimum blood pressure control in our patient.

Keywords: Azole; Posaconazole; Hypertension

Introduction

Posaconazole is a triazole antifungal agent with a broad-spectrum antifungal activity; it is frequently used as prophylaxis and treatment of fungal infections [1]. We here in document posaconazole- induced uncontrolled hypertension in an Allogeneic Hematopoietic Cell Transplant (AHCT) recipient.

Case Presentation

A 68-year-old Caucasian male with past medical history of well controlled essential hypertension (diagnosed in 2003), developed Chronic Myelo Monocytic Leukemia (CMML) in October 2016. While receiving decitabine, fluconazole was initiated for fungal prophylaxis. Development of rash led to switching of fluconazole to posaconazole prophylaxis (300 mg PO daily). At the time of posaconazole initiation his Blood Pressure (BP) was 125/70 mmHg. At this point he was on nebivolol 5 mg daily and valsartan-hydrochlorothiazide 320-25 mg daily. After three weeks of being on posaconazole, his BP began to rise and necessitated dose escalation of nebivolol to 10 mg daily and addition of clonidine 0.2 mg daily per his primary care provider. He underwent a matched unrelated donor transplant following conditioning with fludarabine, melphalan and alemtuzumab in July 2017 and received tacrolimus for Graft Versus-Host Disease (GvHD) prophylaxis. Post-transplant he continued to have uncontrolled hypertension despite titration and adjustment of his antihypertensive medications (Figure 1). His potassium was noted to be at the lower limit of normal despite aggressive potassium repletion (average daily replacement with 60 mEq IV). Initially, elevation of systolic BP to range of 140s to 170s was thought to be related to dexamethasone utilized

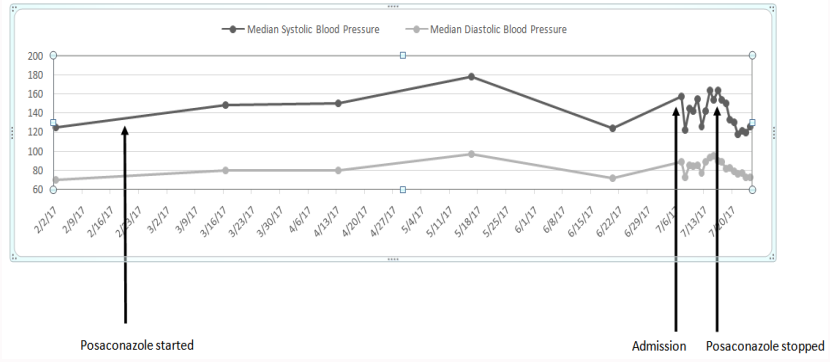

Figure 1: Daily median systolic and diastolic blood pressure measurements from posaconazole initiation to discontinuation.

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Table 1: Rates of hypertension and hypokalemia observed with azoles*.

Azole	Hypertension	Hypokalemia
Fluconazole	NR	< 1%
Itraconazole	3%	2%
Voriconazole	< 2%	1.60%
Posaconazole	11%	22%

* Data per package insert [1,7-9]; NR: Not Reported

Table 2: Summary of case reports published on posaconazole-induced hypertension and/or hypokalemia [3-6,10,11].

Reference	Patient	Dosing	Formulation	Patient Presentation	Proposed Mechanism
Martino, et al. [10]	13 YO F with sarcoma treated for fungal infection	Unintentional overdose	DR tablets	N, bone pain, fatigue, anemia, Hypo-K 2.7 mmol/L	NA
Mahmood, et al. [11]	44 YO M treated for pulmonary histoplasmosis	300 mg daily	DR tablets	Hypo-K 2.2 mmol/L,BP 154/98 mmHg, Fatigue, polyuria	Apparent mineralocorticoid excess
Thompson, et al. [3]	67 YO M treated for chronic cavitary aspergillosis	300 mg daily	DR tablets	Hypo-K 3.4 mmol/L ,BP 165/89 mmHg	Inhibition of 11β-HSD2
Barton, et al. [6]	15 YO M with immunodeficiency syndrome	Prophylactic dose	NA	Hypo-K 2.8 mmol/L ,SBP 160 mmHg	Inhibition of 11β-hydroxylase
Boughton, et al. [4]	67 YO M with MDS	300 mg daily	NA	Hypo-K 2.4 mmol/L ,SBP 150-170 mmHg	Inhibition of 11β-HSD2 and 11β-hydroxylase
Kuriakose, et al. [5]	60 YO F treated for disseminated histoplasmosis	300 mg daily	DR tablets	SOB, orthopnea, pitting pedal edema	Inhibition of 11β-HSD2

11β-HSD2: 11β-Hydroxy Steroid Dehydrogenase type 2; BP: Blood Pressure; DR: Delayed-Release; F: Female; Hypo-K: Hypokalemia; M: Male; MDS: Myelo Dysplastic Syndrome, N: Nausea, NA: Not Addressed; SBP: Systolic Blood Pressure; SOB: Shortness of Breath; YO: Year Old.

for nausea or vomiting prophylaxis and tacrolimus. To control his pressures over the next several days, he was initiated on amlodipine 10 mg, clonidine was increased to twice daily, and he was given as-needed diuretics. However, persistently elevated BP and need for rigorous potassium replacement led to suspicion of posaconazole-induced hypertension, at which point posaconazole was discontinued. Within three days of posaconazole discontinuation, BP started to normalize. Initial reduction in antihypertensive drugs occurred at two days following posaconazole cessation and at time of discharge he needed only amlodipine 5 mg daily, nebivolol 10 mg daily, and clonidine 0.1 mg twice daily for hypertension. His clonidine continued to be titrated down and eventually discontinued. He was not re-challenged with posaconazole. Day +270 post-AHCT, he continues to be in complete remission from CMML with limited chronic GvHD and well controlled hypertension.

Discussion

Though the exact mechanism is unknown, one suggested mechanism of posaconazole-induced hypertension is its selective inhibition of 11β-Hydroxy Steroid Dehydrogenase (11β-HSD) type 2 over 11β-HSD type 1, leading to an increase in cortisol levels and thus activation of aldosterone receptors [2-5]. Another suggested mechanism is the inhibition of the 11β-hydroxylase enzyme, leading to increased levels of 11-deoxy-corticosterone, which also has mineralocorticoid activity [4,6]. Table 1 describes the frequency of hypertension and hypokalemia for various azoles. It should be noted that both hypertension and hypokalemia in AHCT is common due to variety of reasons. Apart from calcineurin-induced hypertension in AHCT patients, thrombotic thrombocytopenic purpura and/or atypical hemolytic uremic syndrome, and posterior reversible encephalopathy syndrome are important serious considerations. Electrolyte abnormalities are common during AHCT and occurrence of correctable hypokalemia without uncontrolled hypertension does not necessitate posaconazole cessation. To our knowledge, there are only six case reports describing hypertension and hypokalemia with posaconazole, five of which were published between 2017 and 2018 [3-11]. These are summarized in Table 2. Ours is the first to describe this phenomenon in AHCT patient. Interestingly, majority of the case reports on posaconazole-induced hypertension and or hypokalemia are in patients who were on the delayed-release tablet formulation, which is known to result in higher plasma concentrations compared to its liquid alternative [1]. We did not check posaconazole levels as the patient was on prophylactic dose. Fortunately, effective alternatives amongst azoles are available today allowing us to switch antifungal.

Conclusion

Recognition of posaconazole-induced hypertension exacerbation requires high index of suspicion in AHCT patients.

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