

2018

Posaconazole-induced hypertension and hypokalemia due to inhibition of the 11 β -hydroxylase enzyme

Kevin Barton

Washington University School of Medicine in St. Louis

T. Keefe Davis

Washington University School of Medicine in St. Louis

Bess Marshall

Washington University School of Medicine in St. Louis

Alexis Edward

Washington University School of Medicine in St. Louis

Neil H. White

Washington University School of Medicine in St. Louis

Follow this and additional works at: https://digitalcommons.wustl.edu/open_access_pubs

Recommended Citation

Barton, Kevin; Davis, T. Keefe; Marshall, Bess; Edward, Alexis; and White, Neil H., "Posaconazole-induced hypertension and hypokalemia due to inhibition of the 11 β -hydroxylase enzyme." *Clinical Kidney Journal*.11,5. 691-693. (2018).
https://digitalcommons.wustl.edu/open_access_pubs/7357



EXCEPTIONAL CASE

Posaconazole-induced hypertension and hypokalemia due to inhibition of the 11 β -hydroxylase enzyme

Kevin Barton¹, T. Keefe Davis¹, Bess Marshall², Alexis Elward³ and Neil H. White²

¹Department of Pediatrics, Division of Nephrology, Washington University, St. Louis, MO, USA, ²Department of Pediatrics, Division of Endocrinology, Washington University, St. Louis, MO, USA and ³Department of Pediatrics, Division of Infectious Disease, Washington University, St. Louis, MO, USA

Correspondence and offprint requests to: T. Keefe Davis; E-mail: davistk@wustl.edu; Twitter handle: @WashU_PedsNeph

Abstract

Posaconazole is an antifungal therapy reported to cause incident hypertension. Hypokalemia is also a known side effect. The combination of hypertension and hypokalemia suggests mineralocorticoid excess. We present the case of a 15-year-old adolescent male with hypertensive urgency while on prophylactic posaconazole therapy for a combined immunodeficiency. We identify the mechanism of posaconazole-induced hypertension to be inhibition of the 11 β -hydroxylase enzyme, resulting in elevated levels of the mineralocorticoid receptor activator deoxycorticosterone. Loss of function of the 11 β -hydroxylase enzyme is responsible for a rare form of congenital adrenal hyperplasia and can be associated with life-threatening adrenal crisis.

Key words: adrenal hyperplasia, 11 β -hydroxylase, hypertension, hypokalemia, mineralocorticoid excess, posaconazole

Introduction and case report

A 15-year-old male adolescent presented to the hospital with hypertensive urgency (systolic readings up to 160 mmHg) and hypokalemia [serum potassium 2.8 mmol/L (normal 3.3–4.9)]. Due to combined immunodeficiency with hypogammaglobulinemia, he was on posaconazole therapy for fungal prophylaxis. He was admitted to the general pediatric ward for further evaluation and management. His blood pressure rose to >200 mmHg systolic and was associated with flushing and headache. He was transferred to the intensive care unit for management with intravenous antihypertensive infusions of nicardipine and esmolol to control blood pressure.

Evaluation for the cause of hypertension included an echocardiogram, magnetic resonance imaging of the brain, abdominal ultrasound with Doppler wave analysis, computerized axial

tomography of the abdomen, serum aldosterone and renin levels, serum chromogranin A and urine 5-hydroxyindoleacetic acid levels for carcinoid syndrome, as well as thyroid studies. All the above studies were normal. Plasma renin and aldosterone levels were low/suppressed (renin 1.2 ng/mL/h, aldosterone <0.4 ng/dL), supporting a hyporeninemic hypertension.

Evaluation for pheochromocytoma was performed due to severe hypertension and episodic flushing. Plasma and urine metanephrines were elevated: normetanephrine 2.7 nmol/L (normal <0.9) and 1372 μ g/24 h (normal <456), respectively. Plasma and urine catecholamines were also elevated three times above the reference range. Because of the elevated metanephrines and catecholamines, he underwent positron emission tomography (PET) nuclear imaging with DOTATATE peptide, which failed to show a somatostatin receptor 2 expressing paraganglioma or

Received: October 10, 2017. Editorial decision: December 12, 2017

© The Author(s) 2018. Published by Oxford University Press on behalf of ERA-EDTA.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Table 1. Hormone, electrolyte levels and blood pressure during and after posaconazole therapy

Test	POSA	POSA off	Normal/therapeutic range
Deoxycorticosterone (ng/mL)	247	24	2–19
11-Deoxycortisol (ng/dL)	2445	167	12–158
Androstenedione (ng/dL)	194	75	33–192
17-Hydroxyprogesterone (ng/dL)	452	215	24–175
Cortisol (mcg/dL)	13	17	3–21
Serum potassium (mmol/L)	2.8	4.3	3.5–4.9
Plasma renin (ng/mL/h)	1.2	NA	1.2–2.4
Plasma aldosterone (ng/dL)	<0.4	NA	<21
Plasma normetanephrine (nmol/L)	2.7	0.28	<0.9
Posaconazole (ng/dL) ^a	3000	NA	>700
Blood pressure (mmHg) ^b	176/72	102/64	<130/80

^aAverage of three levels.

^bAverage of 1 week of measurements.

NA, not available.

pheochromocytoma, ruling out the diagnosis. With the DOTATATE PET not identifying a normetanephrine-secreting tumor, it was concluded that the elevated levels of metanephrine, normetanephrine and catecholamines were elevated due to interference with the assay from esmolol and nicardipine [1].

The possibility of congenital adrenal hyperplasia (CAH) and/or the syndrome of apparent mineralocorticoid excess (AME) was raised. A serum adrenal steroid laboratory panel was sent for analysis. The patient and family did not reveal a history of chronic licorice (glycyrrhizic acid) ingestion. Licorice inhibits the 11 β -hydroxysteroid dehydrogenase type 2 isoform (11 β HSD2). In a review of the literature, it was found that posaconazole inhibits the same enzyme [2]. In this patient, the results of the adrenal steroid panel showed markedly elevated deoxycorticosterone and 11-deoxycortisol levels and androgens (Table 1) suggestive of a block at the level of 11 β -hydroxylase and not AME from inhibition of 11 β -HSD2.

Since he had no prior history of hypertension and no family history of CAH, 11 β -hydroxylase deficiency CAH seemed unlikely. In addition, he previously had an extensive genetic workup of the combined immunodeficiency including whole exome sequencing, which did not identify mutations in either the CYP11B1 gene or the 11 β -HSD2 gene. To evaluate the possibility of hypertension from 11 β -hydroxylase inhibition, posaconazole was stopped. Within 3 weeks of stopping, blood pressure and serum potassium normalized. A repeat adrenal steroid panel off posaconazole showed normal levels of deoxycorticosterone, 11-deoxycortisol and plasma metanephrines (Table 1).

Discussion

This is the first case demonstrating that the mechanism of posaconazole-induced hypertension is inhibition of the 11 β -hydroxylase enzyme. Previous cases of posaconazole-induced hypertension have been hypothesized to be a form of acquired AME due to 11 β -HSD2 inhibition [3]. However, the testing in this patient shows a defect upstream in the adrenal steroidogenesis pathway resulting in elevated deoxycorticosterone and 11-deoxycortisol (Table 1). The supraphysiologic level of deoxycorticosterone activates the mineralocorticoid receptor. This results in excessive activity of the epithelial sodium channel in the distal tubule and collecting duct causing hypertension due to sodium and water retention as well as hypokalemia.

Posaconazole is an antifungal agent that acts by inhibiting fungal cell membrane synthesis by blocking steroidogenesis and depletion of ergosterol in the cell membrane. Adrenal steroid biosynthesis from cholesterol to aldosterone and cortisol is mediated by multiple cytochrome P450 (CYP450) enzymes that include 11 β -hydroxylase. Posaconazole has not previously been reported to specifically inhibit the 11 β -hydroxylase enzyme, but it is an inhibitor of the CYP450 3A4 enzyme [4]. A similar antifungal compound, ketoconazole, has a reported 98% inhibition rate of the 11 β -hydroxylase enzyme at a concentration of 1 μ mol/L [5].

In light of animal studies showing that posaconazole stimulates adrenal cells with an increased incidence of pheochromocytomas [4], our conclusion that metanephrine levels were elevated because of interference with the assay is questionable. Acetaminophen, amoxicillin and sulfa-based drugs are known to interfere with the assays, and he was on trimethoprim with sulfamethoxazole [1, 6]. Beta-adrenergic blockers (esmolol) and calcium channel blockers (nicardipine) increase levels of metanephrines and catecholamines, respectively [1]. Posaconazole likely induced adrenal hyperplasia (which would not be identified by PET imaging), with increased metanephrine and catecholamine levels further compounding hypertension. The return of normal plasma metanephrine levels after stopping posaconazole supports this premise (Table 1).

In conclusion, clinical studies of posaconazole therapy have reported hypokalemia in up to 30% and incident hypertension in 18% of patients [7]. Evaluation of our pediatric patient for secondary hypertension and hypokalemia implicated posaconazole as a cause of mineralocorticoid excess due to 11 β -hydroxylase enzyme inhibition with adrenal hyperplasia. We suggest that those receiving posaconazole therapy be closely monitored for adverse effects. All patients on posaconazole therapy should have screening for hypertension and hypokalemia and, if detected, should undergo further endocrine evaluation accordingly.

Acknowledgement

The authors thank the family for giving permission to discuss this case in the medical literature.

Authors' contributions

K.B. and T.K.D. wrote the first draft of the manuscript. N.W., B.M. and A.E. provided critical revisions to the manuscript.

Conflict of interest statement

None declared.

References

1. Eisenhofer G, Peitzsch M. Laboratory evaluation of pheochromocytoma and paraganglioma. *Clin Chem* 2014; 60: 1486–1499
2. Beck KR, Bächler M, Vuorinen A et al. Inhibition of 11 β -hydroxysteroid dehydrogenase 2 by the fungicides itraconazole and posaconazole. *Biochem Pharmacol* 2017; 130: 93–103
3. Thompson GR, Chang D, Wittenberg RR et al. In vivo 11 β -hydroxysteroid dehydrogenase inhibition in posaconazole-induced hypertension and hypokalemia. *Antimicrob Agents Chemother* 2017; 61: e00760
4. European Medicines Agency. Noxafil: EPAR-Scientific Discussion. London: European Medicines Agency, 2005. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000610/WC500037781.pdf (16 November 2017, date last accessed)
5. Couch RM, Muller J, Perry YS et al. Kinetic analysis of inhibition of human adrenal steroidogenesis by ketoconazole. *J Clin Endocrinol Metab* 1987; 65: 551–554
6. Barco S, Alpigliani MG, Ghiggeri GM et al. Amoxicillin-associated interference in an HPLC-EC assay for urinary fractionated metanephrines: potential pitfall in pheochromocytoma biochemical diagnosis. *Clin Biochem* 2014; 47: 119–121
7. www.micromedexsolutions.com; search term: posaconazole (29 September 2017, date last accessed)