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Authors

Nguyen, Minh-Vu H

Davis, Matthew R

Wittenberg, Rebecca

et al.

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MAJOR ARTICLE

Posaconazole Serum Drug Levels Associated With Pseudohyperaldosteronism

Minh-Vu H. Nguyen,[1] Matthew R. Davis,[2] Rebecca Wittenberg,[2] Ian McHardy,[3] John W. Baddley,[4] Brian Y. Young,[5] Alex Odermatt,[6] and George R. Thompson III[3,7]

[1]Department of Internal Medicine, University of California-Davis Health, Sacramento, California, USA; [2]Department of Pharmacy, University of California-Davis Health, Sacramento, California, USA; [3]Department of Medical Microbiology and Immunology, University of California–Davis Health, Sacramento, California, USA; [4]Department of Internal Medicine, Division of Infectious Diseases, University of Alabama–Birmingham, Birmingham, Alabama, USA; [5]Department of Internal Medicine, Division of Nephrology, University of California–Davis Health, Sacramento, California, USA; [6]Swiss Centre for Applied Human Toxicology and Division of Molecular and Systems Toxicology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland; and [7]Department of Internal Medicine, Division of Infectious Diseases, University of California–Davis Health, Sacramento, California, USA

Background. Posaconazole tablets are well tolerated and efficacious in the prophylaxis and treatment of aspergillosis, mucormycosis, and other invasive fungal infections. There have been case reports of posaconazole-induced pseudohyperaldosteronism (PIPH); however, its occurrence and association with serum posaconazole drug levels have not previously been investigated.

Methods. In this single-center, retrospective, observational study, we examined the occurrence of PIPH in outpatients newly starting posaconazole and evaluated differences in serum posaconazole concentrations and clinical characteristics between those with and without this syndrome.

Results. Sixty-nine patients receiving posaconazole were included, of whom 16 (23.2%) met the definition of PIPH. Patients with PIPH were significantly older (61.1 vs 44.7 years, $P = .007$) and more frequently had hypertension prior to starting posaconazole (68.8% vs 32.1%, $P = .009$). Patients with PIPH had a significantly higher median serum posaconazole level than those without PIPH (3.0 vs 1.2 μg/mL, $P \leq .0001$). There was a positive correlation between serum posaconazole levels and changes in systolic blood pressure ($r = .37$, $P = .01$), a negative correlation between serum posaconazole levels and changes in serum potassium ($r = -.39$, $P = .006$), and a positive correlation between serum posaconazole levels and serum 11-deoxycortisol ($r = .69$, $P < .0001$).

Conclusions. Posaconazole is associated with secondary hypertension and hypokalemia, consistent with pseudohyperaldosteronism, and development is associated with higher serum posaconazole concentrations, older age, and baseline hypertension.

Keywords. toxicity; therapeutic drug monitoring; hypertension; hypokalemia; triazole.

Posaconazole is an extended-spectrum triazole with broad antifungal activity commonly used for the treatment or prophylaxis of aspergillosis, mucormycosis, and other invasive fungal infections [1–4]. Previously, posaconazole was available only as a liquid suspension formulation. A delayed-release tablet has since become available and offers improved bioavailability compared with the solution formulation, is well tolerated, and has a favorable adverse event profile [5, 6]. Recently, however, posaconazole has been noted to cause secondary hypertension, hypokalemia, and occasionally metabolic alkalosis, known as posaconazole-induced pseudohyperaldosteronism (PIPH) [7–13].

The proposed mechanism of PIPH is via inhibition of adrenal 11β-hydroxylase (also known as CYP11B1), 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), or both [7, 8, 13–15]. Inhibition of 11β-hydroxylase results in the accumulation of 11-deoxycorticosterone and 11-deoxycortisol, with mineralocorticoid effects (hypertension, hypokalemia, and alkalosis). Blocking 11β-HSD2 abolishes inactivation of cortisol in the kidney with subsequent glucocorticoid-mediated activation of mineralocorticoid receptors [12, 13, 16].

In this study, we evaluated a cohort of patients who received oral posaconazole tablets for evidence of PIPH and any patient-specific risk factors that may be contributory. Although not previously demonstrated with posaconazole, we hypothesized that like other triazoles [17], there is an association between serum drug concentrations and toxicity, specifically PIPH.

METHODS

We conducted a retrospective case-control study of adult patients who had received the diagnosis of PIPH between 2017 and 2018 and of contemporaneous controls also receiving posaconazole therapy. For inclusion, patients were required

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Correspondence: G. R. Thompson III, 4150 V Street, Suite G500, Department of Internal Medicine, Division of Infectious Diseases, Department of Medical Microbiology and Immunology, University of California-Davis Health (grthompson@ucdavis.edu).

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to have received at least 7 days of posaconazole, had at least 1 posaconazole level measured, and vital signs and laboratory values available following posaconazole initiation. Patients were identified by review of prescription records from the University of California–Davis pharmacies. Inpatients were excluded from analysis due to the confounding effects of intercurrent illness, chemotherapeutic agents, and/or comorbid conditions on blood pressure and serum potassium values. Patients without a return visit to the health system following posaconazole initiation were also excluded. We utilized a standard case report form to obtain data on demographics, underlying diseases, clinical presentation, vital signs, and laboratory values.

We defined a patient with PIPH if they exhibited an increase in systolic blood pressure (SBP) by at least 10 mm Hg and/or a decrease in serum potassium by at least 0.5 mmol/L after starting posaconazole [18, 19]. Blood pressure and potassium changes were calculated as the difference between measurements immediately prior to the first dose of posaconazole and at the next clinical encounter after initiation. Confirmation for PIPH required laboratory testing that showed an elevated 11-deoxycortisol, undetectable plasma aldosterone, and low to low-normal renin activity in the absence of other conditions or medications that may cause similar laboratory values. During the reviewed study period, a subset of our cohort was noted to have been evaluated as part of a quality improvement initiative where all posaconazole patients in that time period were offered screening for PIPH by clinical and laboratory assessment. If patients were suspected to have PIPH, additional laboratory testing (serum renin activity, plasma aldosterone, 11-deoxycortisol, and posaconazole levels) was performed.

We compared demographic data (age, sex, ethnicity), body mass index, comorbidities (diabetes mellitus or preexisting hypertension), creatinine clearance, serum posaconazole concentrations, change in serum bicarbonate levels, daily milligram-per-kilogram dosing, and posaconazole indication between patients with PIPH(+) and those without PIPH(–).

For analysis of the relationship of variables between patients who were diagnosed with or without PIPH, the *t* test or Mann-Whitney *U* test was used for continuous variables; χ^2 or Fisher exact testing was used for categorical variables. The Pearson correlation was used to assess associations between serum posaconazole concentrations, change in SBP, change in potassium, and 11-deoxycortisol if available.

Statistical analyses were conducted using Stata software version 13.1 IC (StataCorp, College Station, TX), using a 2-tailed 5% significance level for all analyses. The University of California–Davis School of Medicine Institutional Review Board approved this study.

RESULTS

Sixty-nine patients met inclusion and exclusion criteria and were included in the cohort, 48% were men, and the median age was 48 years (Table 1). Sixty-seven percent of patients received posaconazole as antifungal prophylaxis in the setting of immunosuppression. Sixteen (23.2%) patients met criteria for PIPH. The median time to diagnosis of PIPH was 46 days (range, 14–96).

PIPH(+) patients were significantly older than PIPH(–) patients; (61.1 vs 44.7 years, $P = .007$). PIPH(+) patients more frequently had hypertension prior to starting posaconazole

Table 1. Differences Among Patients With and Without Posaconazole-Induced Pseudohyperaldosteronism

Variable	PIPH(–) (n = 53)	PIPH(+) (n = 16)	*P* Value
Male, n (%)	25 (47.2)	8 (50.0)	.84
Age, median (IQR), y	44.7 (34.9–57.0)	61.1 (47.3–69.6)	.007
Ethnicity, n (%)			.77
White	31 (58.5)	10 (62.5)	…
Hispanic	13 (24.5)	3 (18.8)	…
Asian	6 (11.3)	3 (18.8)	…
African American	3 (5.7)	0 (0.0)	…
Body mass index, median (IQR), kg/m^2	24.0 (21.3–28.1)	26.2 (22.3–31.9)	.32
Calcineurin inhibitor, n (%)	24 (45)	2 (13)	0.02
Systemic corticosteroid, n (%)	5 (9)	0 (%)	0.58
Diabetes mellitus, n (%)	6 (11.3)	2 (12.5)	>.99
Hypertension,[a] n (%)	17 (32.1)	11 (68.8)	.009
Creatinine clearance, median (IQR), mL/min	102.7 (78.0–126.6)	91.1 (66.6–113.6)	.41
Indicated for antifungal treatment, n (%)[b]	13 (24.5)	10 (62.5)	.005
Posaconazole daily dose, median (IQR), mg/kg	4.7 (3.9–5.4)	4.1 (3.1–4.9)	.11
Serum bicarbonate change, median (IQR), mmol/L	–1 (–3-0)	0 (–1.5–3)	.06
Random serum posaconazole concentration, median (IQR), µg/mL	1.2 (0.8–1.8)	3.0 (2.1–4.1)	<.0001

Abbreviations: IQR, interquartile range; PIPH, posaconazole-induced pseudohyperaldosteronism.

[a]Hypertension was present prior to starting posaconazole.

[b]This variable indicates that posaconazole was prescribed for antifungal treatment as opposed to prophylaxis of an active infection.

compared with patients who were PIPH(–) (68.8% vs 32.1%, P = .009). PIPH(+) patients were also more frequently prescribed posaconazole for active treatment instead of prophylaxis compared with PIPH(–) patients (62.5% vs 24.5%, P = .005). Interestingly, receipt of a calcineurin inhibitor was protective against the development of PIPH [PIPH(+) 13% vs PIPH(–) 45%, P = .02], while systemic corticosteroids had no effect (P = .58). Body mass index, the presence of diabetes, baseline creatinine clearance, and daily milligram-per-kilogram dosing did not differ significantly between groups.

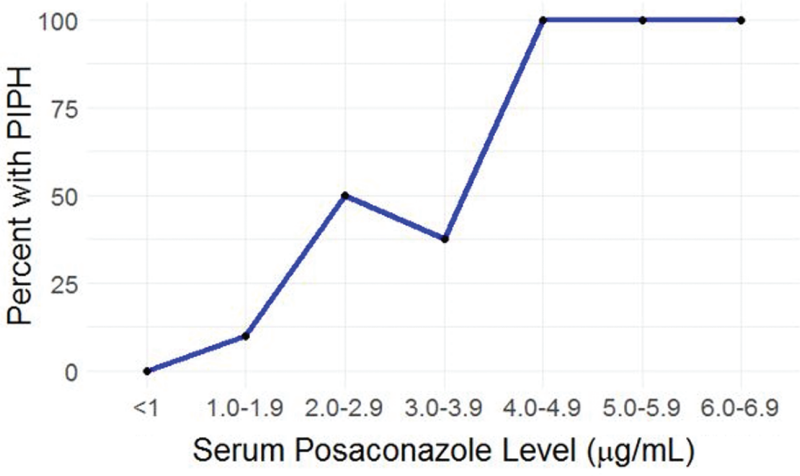
PIPH(+) patients had a significantly higher median serum posaconazole level than PIPH(–) patients (3.0 vs 1.2 μg/mL, P <= .0001), and all patients with posaconazole levels ≥4.0 μg/mL were diagnosed with PIPH (Figure 1), while the development of PIPH in patients with serum posaconazole levels <2.0 μg/mL was uncommon (3/69, 4%; Figure 1).

There was a significant positive correlation between the serum posaconazole level and changes in SBP (r = .37, P = .01; Figure 2A) and a significant negative correlation between serum posaconazole levels and the observed change in serum potassium (r = –.39, P = .006; Figure 2B). There was also a statistically significant positive correlation between serum posaconazole levels and serum 11-deoxycortisol (r = .70, P < .0001; Figure 2C), indicating *CYP11B1* inhibition. Specific endocrinologic laboratory values were available for a subset of patients (n = 35) in this analysis (Figure 2C). These patients had been part of a quality improvement initiative and were offered laboratory "screening" for PIPH or had been assessed for PIPH during their usual care.

There were no significant differences in sex, ethnicity, body mass index, diabetes, creatinine clearance, posaconazole daily milligram-per-kilogram dosing, or changes in serum bicarbonate.

DISCUSSION

Our study reveals an association between serum posaconazole concentrations and an increase in SBP and 11-deoxycortisol, as well as a decrease in serum potassium; all findings confirm the syndrome of pseudohyperaldosteronism. Adverse events associated with serum posaconazole concentrations have only recently been scrutinized. In a recent publication,



Serum posaconazole level	#Pts without PIPH	#Pts with PIPH	Percent of patients with PIPH	Confidence interval	Fisher's Exact Test P value
<1	16	0	0%	0.0-20.6%	NA
1.0-1.9	27	3	10%	2.1-26.5%	0.54
2.0-2.9	5	5	50%	18.7-81.3%	0.004
3.0-3.9	5	3	37.50%	8.5-75.5%	0.03
4.0-4.9	0	2	100%	15.8-100%	0.007
5.0-5.9	0	2	100%	15.8-100%	0.007
6.0-6.9	0	1	100%	2.5-100%	0.06

Figure 1. Serum posaconazole levels and association with the development of posaconazole-induced pseudohyperaldosteronism (PIPH).

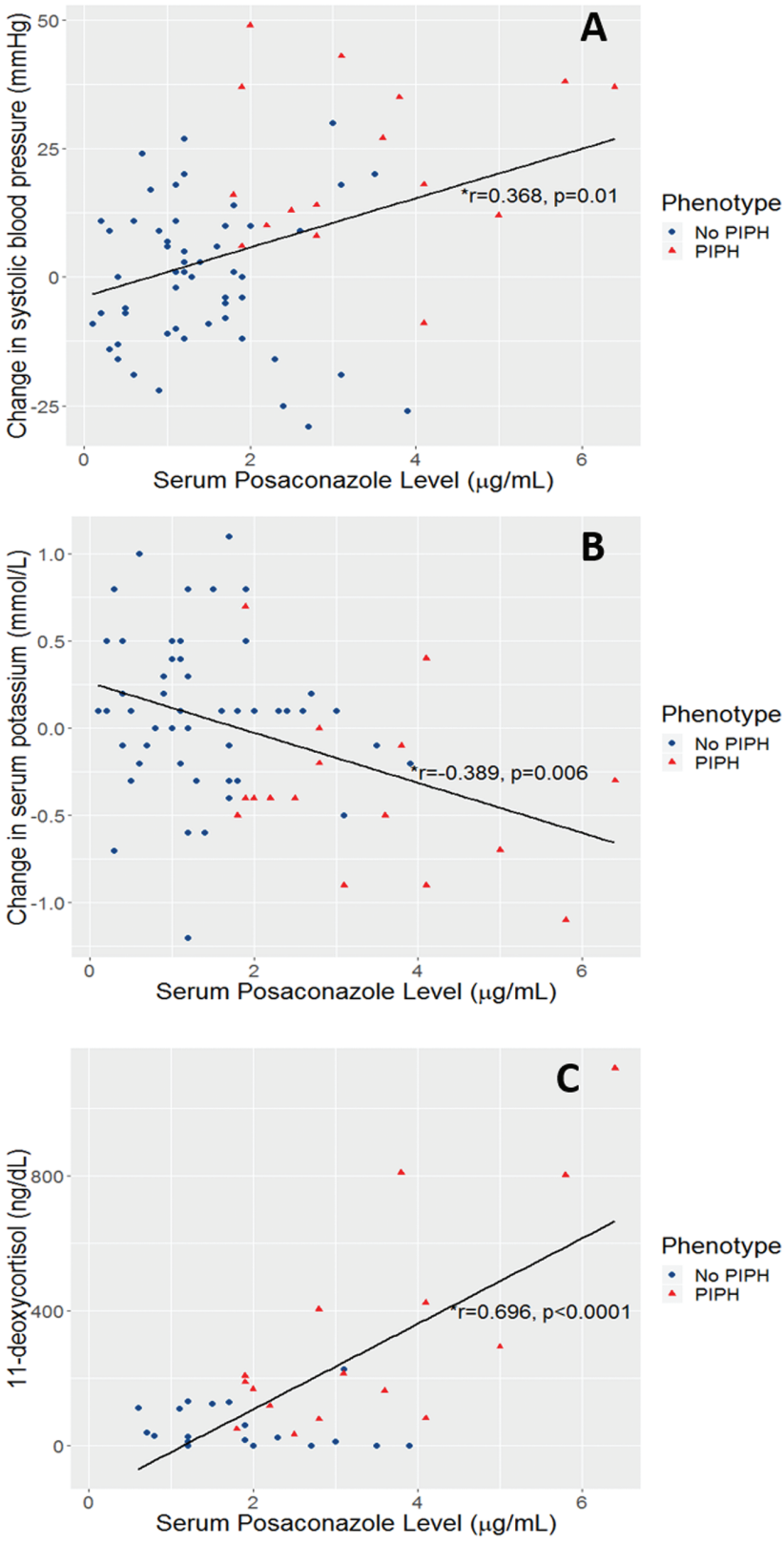


Figure 2. Correlation of posaconazole with clinical and laboratory variables. (*A*) Correlation between serum posaconazole concentration and change in systolic blood pressure (n = 69), (*B*) between serum posaconazole concentration and change in serum potassium (n = 68), and (*C*) between serum posaconazole concentration and serum 11-deoxycortisol (n = 35). Abbreviation: PIPH, posaconazole-induced pseudohyperaldosteronism.

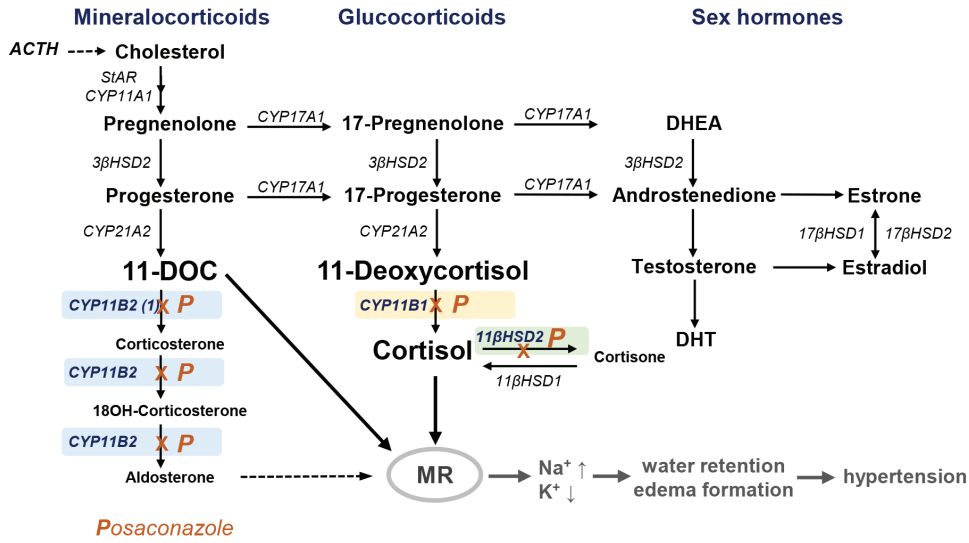


Figure 3. Primary pathway of steroidogenesis and enzyme inhibition by posaconazole (*P*). Inhibition of *CYP11B* and 11βHSD2 leads to excess 11-deoxycorticosterone and cortisol, respectively. Activation of the MR by these hormones results in hypertension and hypokalemia. Abbreviations: 11-DOC, 11-deoxycorticosterone; ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; MR, mineralocorticoid receptor; P, posaconazole.

no association was observed between toxicity and serum drug concentrations [20]. That assessment, however, primarily evaluated patient symptoms, did not include blood pressure as a variable, and queried a clinical database prior to the recognition of PIPH.

Patients with PIPH had a higher median serum posaconazole concentration (3.0 μg/mL) than those without. Notably, serum posaconazole concentrations strongly correlated with the degree of increase in SBP, decrease in serum potassium, and increase in 11-deoxycortisol. These findings corroborate prior case studies of PIPH [7–13, 15] and demonstrate that PIPH occurs with serum drug concentrations that are significantly lower than those described in these prior case reports (median 4.63 μg/mL in accumulated case reports), suggesting this syndrome may be underrecognized. We also emphasize that posaconazole serum concentrations are associated with the development of PIPH, but a definitive therapeutic drug monitoring target recommendation cannot be made given the small number of patients described to date.

Our findings are also helpful in defining the appropriate clinical evaluation of patients with suspected PIPH. Posaconazole is known to inhibit both 11β-hydroxylase and 11β-HSD2 (Figure 3), and the latter syndrome requires an elevated cortisol-to-cortisone ratio for diagnostic confirmation. All patients in our study with laboratory-confirmed PIPH had elevations of serum 11β-deoxycortisol (confirming 11β-hydroxylase inhibition), which obviates additional testing for a possible secondary mechanism potentially sparing additional laboratory/testing expenses. Diagnosis thus rests primarily on the detection of an increase in SBP and a decrease in serum potassium and is confirmed by suppression of renin and aldosterone with a commensurate increase in serum 11-deoxycortisol. Although pseudohyperaldosteronism is frequently associated with an increase in serum bicarbonate, it is not always observed and is not required for diagnosis [7–13].

Our comparative analysis saw age and preexisting hypertension as risk factors for PIPH. This may be secondary to arterial wall thickening resulting in heightened susceptibility to the effects of even small increases in circulating mineralocorticoids, although this remains speculative. Clearly, genomic differences in the genes that encode for 11β-hydroxylase (*CYP11B1*) and 11β-HSD2 (*HSD11B2*) may contribute to the occurrence of PIPH in some patients. Genetic loss-of-function mutations in the *HSD11B2* and *CYP11B1* genes are very rare and result in severe forms of hypertension. A prior case report that described posaconazole-induced hypertension found only wild-type sequences within *HSD11B2* [13]. However, small nucleotide polymorphisms in these genes that might reduce transcriptional expression have been associated with essential hypertension and could potentially aggravate the effect of posaconazole [21–23]. Similarly, interpatient variability in posaconazole tissue concentrations may occur due to differences in transporter expression.

Receipt of a calcineurin inhibitor, however, appeared protective against the development of PIPH in our cohort. Although these agents are known to cause hypertension (via a different mechanism than PIPH) [24], the "protective" effect we observed is not surprising given their propensity to cause hyperkalemia [25, 26]. It is thus possible the hypokalemia observed with PIPH may have been mitigated in patients receiving a concurrent calcineurin inhibitor and thus they would not have fulfilled our PIPH case criteria.

In our analysis, 23% of all patients reviewed were diagnosed with PIPH based on either clinical or laboratory criteria. The true incidence of this syndrome cannot be determined by our retrospective study; however, our findings are similar to the observed rate of hypokalemia (22%) and hypertension (11%) in patients receiving the 300-mg daily tablet formulation [27].

The management of PIPH remains incompletely defined. Patients with ongoing infection and no other treatment options may improve solely with posaconazole dose reduction or the addition of a mineralocorticoid receptor antagonist such as spironolactone. While in other cases an alternative triazole can be prescribed, this alteration alone may abrogate the blood pressure elevation and potassium changes observed with posaconazole therapy.

A key limitation of this study is the possibility for bidirectional sampling bias by including only patients who had posaconazole concentrations available. Providers may have ordered posaconazole serum drug concentrations only in cases of suspected toxicity or in those thought to be at risk for subtherapeutic levels. Inpatients were also excluded from our analysis due to effects of intercurrent illness (eg, neutropenic fever, diarrhea) on blood pressure and potassium levels, and our results may not be generalizable to this population. Another limitation is the difficulty in determining the time to development of PIPH given the differences in time to follow-up between patients in a retrospective study. However, it was seen as soon as 14 days after posaconazole initiation in some patients.

In conclusion, PIPH has only recently been recognized and is associated with higher serum posaconazole blood concentrations. The recognition of this syndrome is paramount to ensure that appropriate management and laboratory evaluation are undertaken.

Notes

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Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health (NIH).

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Potential conflicts of interest. J. W. B. has served as a consultant for Pfizer and Merck. G. R. T. has served as a consultant and received research support from Amplyx, Astellas, Cidara, Mayne, F2G, and Scynexis. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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