

# Posaconazole-Induced Hypertension Due to Inhibition of 11 $\beta$ -Hydroxylase and 11 $\beta$ -Hydroxysteroid Dehydrogenase 2

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We describe two cases of hypertension and hypokalemia due to mineralocorticoid excess caused by posaconazole treatment of coccidioidomycosis and rhinocerebral mucormycosis infections, respectively. Clinical laboratory evaluations, including a comprehensive analysis of blood and urine steroid profiles, revealed low renin and aldosterone and indicated as the underlying mechanism primarily a block of 11 $\beta$ -hydroxylase activity in patient 1, whereas patient 2 displayed weaker 11 $\beta$ -hydroxylase but more pronounced 11 $\beta$ -hydroxysteroid dehydrogenase 2 inhibition. The results show that both previously suggested mechanisms must be considered and emphasize significant interindividual differences in the contribution of each enzyme to the observed mineralocorticoid excess phenotype. The mineralocorticoid symptoms of patient 1 resolved after replacement of posaconazole therapy by isavoconazole, and posaconazole dosage de-escalation ameliorated the effects in patient 2. By providing a thorough analysis of the patients' blood and urine steroid metabolites, this report adds further evidence for two individually pronounced mechanisms of posaconazole-induced hypertension and hypokalemia. The elucidation of the factors responsible for the individual phenotype warrants further research.

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## 1. Case Reports

Recent case reports describing posaconazole-induced mineralocorticoid excess suggested two distinct mechanisms promoting the observed hypertension and hypokalemia: inhibition of the adrenal enzyme 11 $\beta$ -hydroxylase [1, 2] or the peripheral cortisol metabolizing 11 $\beta$ -hydroxysteroid dehydrogenase 2 (11 $\beta$ -HSD2) [2–5]. The majority of these studies did not evaluate the patient's steroid profile in blood and urine, allowing only a limited understanding of the relative contribution of the two enzymes leading to the drug-induced hypertension and hypokalemia. Therefore, we conducted a detailed analysis of blood and urine steroid metabolites for the two presented cases to address this issue.

Abbreviations: 11 $\beta$ -HSD2, 11 $\beta$ -hydroxysteroid dehydrogenase 2; 11-DHC, 11-dehydrocorticosterone; 11-DOC, 11-deoxycorticosterone; UHPLC-MS/MS, ultra-high-performance liquid chromatography–tandem mass spectrometry.

## 2. Patient 1

A 54-year-old man with no past medical history presented with fever, chills, cough, and weight loss. His initial examination, vital signs (blood pressure 127/90 mm Hg), and chemistry and laboratory values (chem 10 test, liver function profile) were normal with the exception of positive serologic testing for coccidioidomycosis. Therefore, he was placed on fluconazole 600 mg daily. However, over the next 6 weeks he developed nausea and cheilitis and xerosis that were attributed to fluconazole therapy, and he was transitioned to posaconazole 300 mg daily. His systemic and respiratory symptoms improved; however, he developed new-onset hypertension (163/94 mm Hg) and hypokalemia (3.1 mmol/L) 8 weeks after starting posaconazole therapy. Besides posaconazole, he received only pantoprazole.

Because of suspected posaconazole-induced mineralocorticoid excess, an initial clinical laboratory evaluation was obtained, revealing very low renin (0.2 ng/mL/h) and undetectable aldosterone values (<3.0 ng/dL) but elevated concentrations of estradiol (49 pg/mL) and 11-deoxycortisol (320 ng/dL) and a posaconazole serum blood concentration of 3.1  $\mu$ g/mL. Serum electrolyte concentrations were normal with the exception of continued hypokalemia (3.0 mmol/L). Treatment was continued and serum was obtained again 4 weeks later, with posaconazole levels of 2.7  $\mu$ g/mL at that time. To gain closer insight into the mechanism of the posaconazole-induced mineralocorticoid excess, a comprehensive serum (Table 1) and urinary (Table 2) steroid analysis was performed with ultra-high-performance liquid chromatography–tandem mass spectrometry (UHPLC-MS/MS). The results confirmed serum aldosterone concentrations below the limit of detection, low corticosterone (42 ng/dL) and androstenedione (45 ng/dL) concentrations, and moderately elevated concentrations of 11-deoxycortisol (216 ng/dL) (Table 1), suggesting inhibition of 11 $\beta$ -hydroxylase. Normal serum levels were detected for cortisol (7.4  $\mu$ g/dL), cortisone (1.65  $\mu$ g/dL), 11-dehydrocorticosterone (11-DHC) (36 ng/dL), 11-deoxycorticosterone (11-DOC) (8.3 ng/dL), 17-hydroxyprogesterone [17-OH progesterone (102 ng/dL)], testosterone (242 ng/dL), and androstenedione (46 ng/dL).

Analysis of 24-hour urine revealed undetectable levels of aldosterone and very low tetrahydroaldosterone (4.95  $\mu$ g/24 h) but normal concentrations of cortisol (111  $\mu$ g/24 h), cortisone (113  $\mu$ g/24 h), and their tetrahydro-metabolites (Table 2). Importantly, urinary 11-deoxycortisol (1.99  $\mu$ g/24 h) and 11-DOC (2.96  $\mu$ g/24 h) were markedly elevated, supporting an inhibition of 11 $\beta$ -hydroxylase. 17-OH progesterone (2.11  $\mu$ g/24 h) was slightly elevated, and androgen metabolites were normal or low. Creatinine from the 24-hour urine collection was 61 mg/dL, and total creatinine 1552 mg.

**Table 1. Detailed Analysis of Steroids in Blood From Posaconazole-Treated Patients**

| Steroid                   | Patient 1        | Patient 2         | Reference Range |
|---------------------------|------------------|-------------------|-----------------|
| Aldosterone, ng/dL        | nd               | nd                | 2.0–18          |
| Cortisol (F), $\mu$ g/dL  | 7.4              | 5.2               | 5.0–25          |
| Cortisone (E), $\mu$ g/dL | 1.65             | 0.19 <sup>a</sup> | 1.0–3.5         |
| F/E                       | 4.5              | 27 <sup>b</sup>   | 2–8             |
| Corticosterone (B), ng/dL | 42 <sup>a</sup>  | 54 <sup>a</sup>   | 62–1600         |
| 11-DHC (A), ng/dL         | 36               | 6.5               | nr              |
| B/A                       | 1.16             | 8.3               | nr              |
| 11-deoxycortisol, ng/dL   | 216 <sup>b</sup> | 186 <sup>b</sup>  | <158            |
| 11-DOC, ng/dL             | 8.3              | 3.2               | 2.0–19          |
| Testosterone, ng/dL       | 242              | 32 <sup>a</sup>   | 200–1070        |
| Androstenedione, ng/dL    | 46               | 3.8 <sup>a</sup>  | 30–250          |
| 17-OH progesterone, ng/dL | 101              | 36                | 5–250           |

Steroids were quantified in a serum sample and a whole blood sample from patient 1 and patient 2, respectively. Samples were collected at 8 AM and analyzed by UHPLC-MS/MS [6]. Reference ranges are for men, age 20–50, samples taken between 8 and 10 AM, supine position [7, 8].

Abbreviations: nd, below lower limit of detection; nr, not reported.

<sup>a</sup>Below normal range.

<sup>b</sup>Above normal range.

**Table 2. Comprehensive Analysis of Steroids in Urine From Posaconazole-Treated Patients**

| Steroid                 | Patient 1                                   |   | Patient 2             |   | Range                                       |
|-------------------------|---|---|-----------------------|---|---|
|                         | 24-h Urine<br>( $\mu\text{g}/24\text{ h}$ ) | 24-h Urine<br>Normalized to<br>CRT $\times 10^{-6}$ | Spot Urine<br>(ng/mL) | Spot Urine<br>Normalized to<br>CRT $\times 10^{-6}$ | 24-h Urine<br>( $\mu\text{g}/24\text{ h}$ ) |
| Cortisol (F)            | 111   | 71  | 57                    | 60  | 35–168                                      |
| Cortisone (E)           | 113   | 73  | 29.5                  | 31 <sup>a</sup>                                     | 92–366                                      |
| F/E                     | 0.98 <sup>b</sup>                           |   | 1.95 <sup>b</sup>     |   | 0.28–0.85                                   |
| a-THF                   | 626 <sup>a</sup>                            | 403   | 612                   | 644 <sup>a</sup>                                    | 796–2456                                    |
| b-THF                   | 1647  | 1061  | 1214                  | 1277  | 942–2800                                    |
| a-THE                   | 69  | 44  | 22.1                  | 23 <sup>a</sup>                                     | 62–752                                      |
| b-THE                   | 2569  | 1655  | 516                   | 543 <sup>a</sup>                                    | 1365–5788                                   |
| sumTHF/sumTHE           | 0.86  |   | <sup>b</sup> 3.39     |   | 0.66–1.44                                   |
| Corticosterone (B)      | 6.35 <sup>b</sup>                           | 4.1   | 2.21                  | 2.33  | 0.2–4.8                                     |
| 11-DHC (A)              | 12.4  | 8.0   | 3.11                  | 3.27 <sup>a</sup>                                   | 6–40  |
| B/A                     | 0.51  |   | 0.71                  |   | nr  |
| b-THB                   | 348 <sup>b</sup>                            | 224   | 392                   | 413   | 40–326                                      |
| a-THB                   | 370   | 238   | 119                   | 126   | 86–588                                      |
| b-THA                   | 220 <sup>b</sup>                            | 142   | 21.8                  | 23  | 3–65  |
| a-THA                   | 58 <sup>b</sup>                             | 37  | 24.1                  | 25  | 2–29  |
| sumTHB/sumTHA           | 2.58  |   | 11.1                  |   |   |
| 11-Deoxycortisol        | 1.99 <sup>b</sup>                           | 1.28  | 1.24                  | 1.31 <sup>b</sup>                                   | <0.5  |
| 11-Deoxy-corticosterone | 2.96 <sup>b</sup>                           | 1.91  | 1.37                  | 1.44 <sup>b</sup>                                   | 0.1–0.5                                     |
| Aldosterone             | nd <sup>a</sup>                             | nd  | nd                    | nd <sup>a</sup>                                     | 2.3–21                                      |
| TH-aldo                 | 4.95 <sup>a</sup>                           | 3.19  | nd                    |   | 6–79  |
| 18-OH-F                 | 23 <sup>a</sup>                             | 15  | 2.74                  | 2.88 <sup>a</sup>                                   | 51–515                                      |
| 18-OH-corticosterone    | 9.87 <sup>b</sup>                           | 6.4   | 1.30                  | 1.37  | 1.5–6.5                                     |
| a-Cortolone             | 1489  | 959   | 263                   | 276 <sup>a</sup>                                    | 333–1667                                    |
| b-Cortolone             | 976   | 629   | 185                   | 194   | 249–1049                                    |
| b-Cortol                | 579 <sup>b</sup>                            | 373   | 256                   | 270   | 70–336                                      |
| Testosterone            | 6.87  | 4.4   | 0.56                  | 0.59 <sup>a</sup>                                   | 3–47  |
| Androstenedione         | 19.9 <sup>a</sup>                           | 12.8  | 2.62                  | 2.76 <sup>a</sup>                                   | 50–220                                      |
| Etiocholanolone         | 1406  | 906   | 192                   | 202   | 430–3300                                    |
| Androsterone            | 1315  | 847   | 271                   | 285   | 320–5400                                    |
| 17-OH-progesterone      | 2.11 <sup>b</sup>                           | 1.4   | 1.40                  | 1.47  | 0.2–1.5                                     |
| 11-Keto-etiocholanolone | 315   | 203   | nd                    | nd <sup>a</sup>                                     | 79–1026                                     |
| 11b-OH-etiocholanolone  | 864   | 557   | 39                    | 41 <sup>a</sup>                                     | 18–1034                                     |
| 11b-OH-androsterone     | 113 <sup>a</sup>                            | 73  | 26                    | 27 <sup>a</sup>                                     | 500–1733                                    |
| Progesterone            | 2.62 <sup>a</sup>                           | 1.69  | 1.47                  | 1.55  | nr  |
| Dehydroepiandrosterone  | 9.46 <sup>a</sup>                           | 6.1   | 1.54                  | 1.62 <sup>a</sup>                                   | 21–2710                                     |
| Creatinine              | 0.61 mg/mL                                  |   | 0.95 mg/mL            |   | 0.63–2.50 g/24 h                            |

Steroids were quantified in a 24-h urine sample and a spot urine sample from patient 1 and patient 2, respectively, by UHPLC-MS/MS. Total urine volume: 2550 mL. Reference ranges are for men, age 20–50 [8–10].

Abbreviations: 11-DHC, 11-dehydrocorticosterone; CRT, creatinine; E, cortisone; F, cortisol; nd, below lower limit of detection; nr, not reported; OH, hydroxy; TH-aldo, tetrahydroaldosterone; THA, tetrahydro-11-dehydrocorticosterone; THB, tetrahydrocorticosterone; THE, tetrahydrocortisone; THF, tetrahydrocortisol.

<sup>a</sup>Below normal range.

<sup>b</sup>Above normal range.

Posaconazole therapy was discontinued, and isavuconazole (186 mg daily) was initiated. On follow-up 6 weeks later, the patient's hypertension and hypokalemia had resolved (134/92 mm Hg and 4.3 mmol/L, respectively).

### 3. Patient 2

A 73-year-old man with a past medical history of multiple myeloma presented 3 months after initiation of dexamethasone and chemotherapy. He complained of left eye swelling and pain of 1 week's duration and was found on MRI to have maxillary sinus thickening with erosion and

inflammation of the surrounding structures, including the orbit. He immediately underwent surgical evaluation and received a diagnosis of rhinocerebral mucormycosis (*Rhizopus* spp identified on cultures and histopathology of the resected tissue). He underwent left orbital exenteration and maxillectomy and was treated with liposomal amphotericin B and micafungin for 21 days. He was thereafter transitioned to oral posaconazole 300 mg daily and discharged after 72 hours of observation and repeated surgical intervention showing no further evidence of infection.

Upon outpatient follow-up, ~9 weeks later, he was noted to have new onset of hypertension (blood pressure 154/69 mm Hg) and hypokalemia (3.3 mmol/L). All other vital signs were within normal limits. Besides posaconazole, this patient received filgrastim, sitagliptin, pantoprazole, and oxycodone. Physical examination found postoperative changes, left facial numbness, and no signs of ongoing infection. Laboratory evaluation revealed low renin (0.36 ng/mL/h), undetectable aldosterone (<2 ng/dL), and elevated 11-deoxycortisol (406 ng/dL) concentrations and a serum osmolality of 292 mOsm/kg, indicating mineralocorticoid excess due to posaconazole-dependent inhibition of 11 $\beta$ -hydroxylase. Furthermore, serum posaconazole levels were high (5.0  $\mu$ g/mL), and estradiol concentrations were below the limit of detection (<15 pg/mL). Urine analyses at this time revealed spot osmolality of 292 mOsm/kg and potassium of 23.9 mmol/L, confirming a transtubular potassium gradient of 7.24.

The patient's posaconazole dosage was then reduced to 200 mg/d. However, after 4 weeks of this treatment, renin and aldosterone levels were found to be further dramatically decreased (<0.1 ng/mL/h and <2 ng/dL, respectively), and posaconazole concentrations were still elevated (3.3  $\mu$ g/mL) but lower compared with the last visit, and estradiol levels stayed comparably low (<15 pg/mL). Again, further comprehensive blood steroid analyses were performed and revealed normal concentrations of cortisol (5.2  $\mu$ g/dL) and 11-DOC (3.2 ng/dL), low levels of corticosterone (54 ng/dL), and clearly decreased levels of cortisone (0.19  $\mu$ g/dL) and 11-DHC (6.5 ng/dL) (Table 1). 11-Deoxycortisol levels (186 ng/dL) were confirmed to be slightly elevated. However, cortisol to cortisone (27) and corticosterone to 11-DHC ratios (8.4) were markedly increased, indicating potent inhibition of 11 $\beta$ -HSD2. Testosterone and androstenedione were very low, whereas 17-OH progesterone was normal.

Analysis of spot urine revealed elevated ratios of cortisol to cortisone (1.95) and their tetrahydro-metabolites (3.39), supporting 11 $\beta$ -HSD2 inhibition (Table 2). Aldosterone and tetrahydroaldosterone were not detectable, whereas a qualitative analysis after normalization to creatinine suggested elevated levels of 11-deoxycortisol and 11-DOC, supporting partial inhibition of 11 $\beta$ -hydroxylase. Spot urine creatinine was 95 mg/dL.

Subsequently, his daily posaconazole dosage was lowered to 100 mg, and 3 weeks later his serum posaconazole level had further decreased to 1.68  $\mu$ g/mL, his blood pressure had normalized to 130/76 mm Hg, and his potassium normalized at 4.4 mmol/L. The patient declined further laboratory evaluation due to the expense.

#### 4. Discussion

The occurrence of hypertension and hypokalemia as adverse effects of posaconazole treatment has been reported in market authorization studies [6]. Nevertheless, only recently have several case studies addressed the mechanism underlying the symptoms of mineralocorticoid excess in more detail, with some debate about the predominantly affected enzyme [1, 2, 4, 5, 12–14]. Whereas some reports proposed 11 $\beta$ -HSD2 to be the cause of apparent mineralocorticoid excess [4, 5], others suggested 11 $\beta$ -hydroxylase to be responsible for the observed phenotype [1].

The detailed analyses of blood and urine steroids in the two presented cases allowed us to unravel the relative contribution of the two enzymes to the posaconazole-induced low-renin, low-aldosterone hypertension and hypokalemia. The elevated 11-deoxycortisol and 11-DOC concentrations along with normal or only slightly elevated ratios of cortisol to cortisone and their tetrahydro-metabolites indicate inhibition of CYP11B1 (and CYP11B2) as the predominant cause in patient 1, with weak or negligible inhibition of 11 $\beta$ -HSD2. In contrast, the markedly elevated ratios of active to inactive glucocorticoids, in both blood and urine, indicate

pronounced inhibition of 11 $\beta$ -HSD2 in patient 2. Additionally, the moderately increased 11-deoxycortisol revealed that CYP11B1 (and CYP11B2) was at least partially inhibited.

Patients with mineralocorticoid excess phenotype were found to generally exhibit high serum posaconazole concentrations (>2.5  $\mu$ g/mL). The factors responsible for the increased serum levels and for the differential inhibition of CYP11B1/2 and 11 $\beta$ -HSD2 are not fully understood. The interindividual differences for the enzymatic inhibition may be explained by different distribution volumes limiting the concentrations of posaconazole reached in the adrenals, necessary to inhibit 11 $\beta$ -hydroxylase, compared with those in the kidney or colon, important for 11 $\beta$ -HSD2 inhibition.

Posaconazole is metabolized mainly by glucuronidation via UGT1A4 and a potent inhibitor of CYP3A4 and a substrate/inhibitor of the P-glycoprotein efflux transporter [15–17]. Thus, comedication must be carefully monitored. Regarding the two presented cases, comedication was unlikely to be a contributing factor to the onset of hypertension. Both patients received the proton pump inhibitor pantoprazole, which increases gastric pH, thereby potentially reducing the adsorption of posaconazole upon oral intake. No interactions with posaconazole are known for filgrastim and sitagliptin. A reduced metabolism of oxycodone by CYP3A4 might have been occurred, however, promoting opioid-dependent adverse effects rather than the mineralocorticoid excess. Furthermore, the bioavailability of posaconazole may be increased by reduced binding to serum albumin (>98% under normal conditions) in situations of severe inflammation or reduced liver and kidney function [18] or by genetic polymorphisms in metabolism (UGT1A4) and transport (P-glycoprotein) or altered expression of these proteins.

The two cases emphasize detailed blood and urine steroid analyses (especially quantification of aldosterone, tetrahydroaldosterone, cortisol, cortisone, their tetrahydro-metabolites, 11-DOC, and 11-deoxycortisol) to unravel the underlying mechanism of the posaconazole-induced hypertension and hypokalemia. Two distinct mechanisms (*i.e.*, inhibition of 11 $\beta$ -hydroxylase and 11 $\beta$ -HSD2) were found to be responsible for posaconazole-induced pseudohyperaldosteronism, with significant interindividual differences. Careful consideration of comedications affecting the pharmacokinetics and pharmacodynamics is warranted. In addition, further research on the impact of susceptibility factors such as polymorphisms in genes encoding for proteins involved in metabolism or transport of posaconazole is needed.

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**Disclosure Summary:** The authors have nothing to disclose.

**Data Availability:** All data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

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