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Editorial Comment

EDITORIAL COMMENT

Unravelling drug-induced hypertension: molecular mechanisms of aldosterone-independent mineralocorticoid receptor activation by posaconazole

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ABSTRACT

Drug-induced hypertension offers the opportunity to further understand pathways involved in the regulation of blood pressure. Posaconazole is an antifungal agent known to induce hypertension and hypokalaemia. In recent months, a flurry of reports has unravelled the metabolic processes involved. In this issue of *CKJ*, Barton K, Davis TK, Marshall B *et al.* Posaconazole-induced hypertension and hypokalemia due to inhibition of the 11β-hydroxylase enzyme. *Clin Kidney J* 2018; 11: 691–693 present convincing evidence of 11β-hydroxylase inhibition resulting in a biochemical syndrome resembling genetic congenital adrenal hyperplasia and characterized by high 11-deoxycorticosterone and 11-deoxycortisol levels as well as androgen levels. This adds to prior evidence supporting inhibition of 11β-hydroxysteroid dehydrogenase 2, the enzyme that inactivates cortisol in aldosterone-sensitive tissues such as the kidneys, yielding a syndrome resembling genetic apparent mineralocorticoid excess or licorice toxicity, characterized by a high cortisol/cortisone ratio.

Keywords: antifungal, drug-induced hypertension, 11-deoxycortisol, 11β-hydroxylase, 11β-hydroxysteroid dehydrogenase 2

Posaconazole is a triazole antifungal drug, structurally similar to fluconazole, itraconazole and voriconazole. In Europe, it is approved to treat invasive aspergillosis, fusariosis, chromoblastomycosis, mycetoma and coccidioidomycosis, when treatments with other antifungal medicines (amphotericin B, itraconazole or fluconazole) cannot be tolerated or have failed, and to prevent invasive fungal infections in immunocompromised patients [1]. Although hypertension and hypokalaemia are listed as common adverse effects and high blood pressure was already noted in preclinical studies, it was not until 2017 that insights into the molecular mechanisms of posaconazole-induced hypertension were published [2–6]. A virtual screening of drugs inhibiting 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2, corticosteroid 11β-dehydrogenase isozyme 2), followed by biological assessment of selected hits, identified itraconazole [half maximal inhibitory concentration (IC50) 139 ± 14 nM] and posaconazole (IC50 460 ± 98 nM) as potent inhibitors of human 11β-HSD2 in cell lysates, although activity against rodent 11β-HSD2 was considerably lower [2]. The IC50 for posaconazole is well within the maximum serum concentration (C_{max}) of around 700 nM following a single 200 mg dose [7]. Additionally, in this issue of CKJ, Barton *et al.* present convincing evidence of 11β-hydroxylase inhibition in a well-characterized patient [8]. Overall, the picture that has emerged is that of dose-dependent hypertension associated with hypokalaemia, metabolic alkalosis and suppressed renin and aldosterone levels [3–6, 8], which

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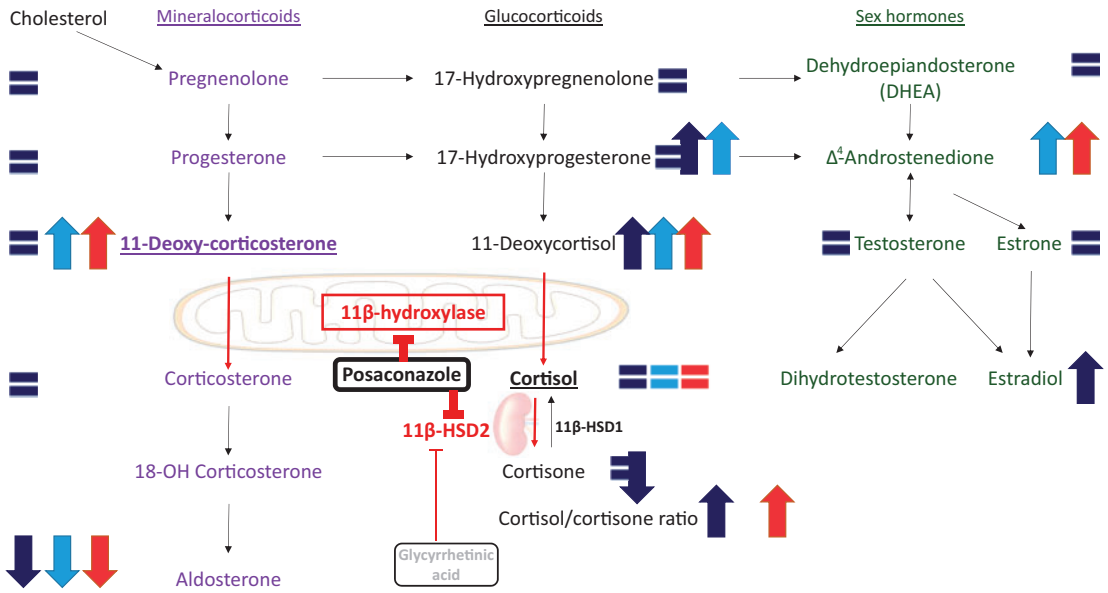

FIGURE 1: Human *in vivo* evidence of posaconazole inhibition of the mitochondrial enzyme 11β-hydroxylase and of kidney 11β-HSD2 driving aldosterone-independent MR activation causing hypertension and hypokalaemia. Target enzymes are in red and bold, molecules (11-deoxycorticosterone, cortisol) potentially driving MR activation in patients on posaconazole are in bold and underlined. The MR-activating effect of cortisol will only be noticed in tissues dependent on 11β-HSD2 to degrade cortisol and prevent cortisol activation of the receptor, such as the kidney. Arrows indicate whether specific metabolites were found increased, decreased or within the normal range (=) by the three recent case reports, which are colour coded in dark blue [4], light blue [8] and red [5]. 11β-HSD2 is also inhibited by glycyrrhetinic acid, a metabolite generated *in vivo* from glycyrrhizic acid present in licorice [9].

has been variously described as apparent mineralocorticoid excess (AME) [4], pseudohyperaldosteronism [6] or adrenal hyperplasia [8].

WHAT IS 11β-HYDROXYLASE?

11β-hydroxylase, encoded by the *CYP11B1* gene, is a mitochondrial enzyme catalysing the addition of a hydroxyl group to 11-deoxycorticosterone and 11-deoxycortisol to yield corticosterone and cortisol, respectively (**Figure 1**). Inactivating mutations in *CYP11B1* cause a rare form of autosomal recessive congenital adrenal hyperplasia, characterized by aberrant sex steroid production, leading to virilization of female newborns, and, in both the genders, advanced bone ages and hypertension [10]. A high 11-deoxycortisol level is the most robust diagnostic biochemical marker.

WHAT IS 11β-HSD2?

11β-HSD2, encoded by the *HSD11B2* gene, oxidizes cortisol to the inactive metabolite cortisone, thus preventing activation of the mineralocorticoid receptor (MR) by cortisol, which circulates at 100- to 1000-fold higher concentrations than aldosterone, and binds with equal affinity to the MR [9]. 11β-HSD2 is mainly expressed by aldosterone-sensitive tissues, such as the kidneys, to prevent physiological cortisol levels from activating the MR. At the endoplasmic reticulum membrane it functionally interacts with the MR [11]. 11β-HSD2 inactivation results in physiological cortisol levels fully activating MR-driven kidney responses leading to aldosterone-independent MR activation. Indeed, inactivating mutations cause autosomal recessive AME, which disappears following kidney transplantation [12]. An elevation in the urinary tetrahydrocortisol (THF) plus allo-THF to tetrahydrocortisone (THE) [(THF + allo-THF)/THE] ratio is pathognomonic of homozygous inactivation, but it was reported to be less sensitive than a high serum cortisol/cortisone ratio to detect heterozygous subjects with milder enzyme deficiency [13]. 11β-HSD2 is also inhibited by glycyrrhetinic acid, a metabolite generated *in vivo* from glycyrrhizic acid present in licorice, which causes aldosterone-independent MR activation [14]. Mild 11β-HSD2 defects have been suggested to contribute to essential hypertension [9].

11β-HSD2 is also expressed at high level in the placenta, where it is thought to regulate the passage of maternal active glucocorticoids into the fetal circulation and maternal-fetal electrolyte and water transport [12].

WHAT IS THE EVIDENCE FOR POSACONAZOLE INHIBITION OF 11β-HSD2 AND OF 11β-HYDROXYLASE?

Three recent reports have described a syndrome of excess MR activation characterized by hypertension, hypokalaemia, suppressed renin and aldosterone levels, and evidence of inhibition of mitochondrial 11β-hydroxylase and, less convincingly, of 11β-HSD2 (Figure 1).

Thompson *et al.* observed reversible increases in 11-deoxycortisol levels as well as a high cortisol/cortisone ratio, that is, evidence of both 11β-hydroxylase and 11β-HSD2 inhibition, within weeks of initiating posaconazole therapy [4].

In this issue of *CKJ*, Barton *et al.* present convincing evidence of 11β-hydroxylase inhibition in a well-characterized patient [8]. Marked elevations in deoxycorticosterone, 11-deoxycortisol and androgens were observed in the absence of mutations in *HSD11B2* or *CYP11B1*, and these changes were reversible upon posaconazole withdrawal. This also answers the question whether genetic variants in either *HSD11B2* or *CYP11B1* may render the individual more sensitive to posaconazole-induced hypertension. Unfortunately, the cortisol/cortisone ratio was not explored.

Boughton *et al.* observed very high 11-deoxycorticosterone and 11-deoxycortisol levels, high androstenedione levels and increased

serum cortisol/cortisone ratio, again suggestive of both 11β-hydroxylase and 11β-HSD2 inhibition [5]. They also documented bilateral adrenal hyperplasia. However, they did not document the reversibility of biochemical changes upon posaconazole withdrawal. The patient improved on spironolactone.

WHAT IS THE EXPLANATION FOR THE DIVERGENT FINDINGS?

A key difference between the three reports is the finding by Thompson *et al.* of normal adrenocorticotropic hormone (ACTH) and 11-deoxycorticosterone levels, in contrast to the high level reported by Boughton and (for 11-deoxycorticosterone) by Barton *et al.* [4, 5, 8]. One possibility relates to the time-course. Thompson *et al.* studied their patient a few weeks into posaconazole therapy, while the Boughton patient had been on long-term prophylactic posaconazole and although Barton's timing is unclear, the prophylactic prescription also suggests long-time use. Longer therapy may favour adaptive responses such as increased ACTH levels that drive up the level of upstream molecules.

Thompson and Boughton found high serum cortisol/cortisone ratios suggestive of 11β-HSD2 inhibition, but only Boughton studied urinary ratios of their metabolite, which were normal, arguing against severe 11β-HSD2 inhibition [13]. Further studies in this regard are needed.

ARE THESE PATIENTS AT RISK OF ADRENAL INSUFFICIENCY?

Despite normal cortisol levels, the abnormally low cortisol response to ACTH stimulation conveys risk of suboptimal response to stress [5]. This should be taken into account in the care of these patients.

IS THERE A ROLE FOR CATECHOLAMINES IN HYPERTENSION?

Barton *et al.* observed high catecholamine and metanephrine levels that may or may not have been related to concurrent medications [8]. Interestingly, 11BHSD2$^{-/-}$ (11β-HSD2-deficient) mice develop over time hypertension characterized by high urinary catecholamine levels that is responsive to α1-adrenergic receptor blockade [15], while high norepinephrine levels have been reported in 11β-hydroxylase-deficient individuals [16]. Careful analysis of patients on and off posaconazole may provide further insights into the connections between cortisol pathway enzymes and catecholamines.

CONCLUSION

In conclusion, three recent case reports addressing different and complementary aspects of posaconazole-induced hypertension with hypokalaemia converge on aldosterone-independent MR activation and dismiss previous suggestions of intestinal losses driving hypokalaemia. A correct understanding of the pathogenic mechanisms avoids unnecessary diagnostic workups in routine clinical care and offers the possibility of further research to unravel the pathophysiology of 11β-HSD2 and 11β-hydroxylase and their connection to catecholamines, by taking advantage of the reversible nature of posaconazole prescription and of the different therapeutic and prophylactic regimens in clinical use.

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