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Antifungal therapy with azoles and the syndrome of acquired mineralocorticoid excess

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ABSTRACT

The syndromes of mineralocorticoid excess describe a heterogeneous group of clinical manifestations leading to endocrine hypertension, typically either through direct activation of mineralocorticoid receptors or indirectly by impaired pre-receptor enzymatic regulation or through disturbed renal sodium homeostasis. The phenotypes of these disorders can be caused by inherited gene variants and somatic mutations or may be acquired upon exposures to exogenous substances. Regarding the latter, the symptoms of an acquired mineralocorticoid excess have been reported during treatment with azole antifungal drugs. The current review describes the occurrence of mineralocorticoid excess particularly during the therapy with posaconazole and itraconazole, addresses the underlying mechanisms as well as inter- and intra-individual differences, and proposes a therapeutic drug monitoring strategy for these two azole antifungals. Moreover, other therapeutically used azole antifungals and ongoing efforts to avoid adverse mineralocorticoid effects of azole compounds are shortly discussed.

1. Introduction

The management and prevention of hypertension represents an important global health challenge. Hypertension is the leading preventable risk factor for premature morbidity and mortality worldwide (Mills et al., 2016). While the majority of patients suffering from hypertension are diagnosed with primary, idiopathic hypertension, secondary forms of hypertension with a specific underlying cause for the blood pressure (BP) elevation are less frequently identified. The causes of secondary hypertension include in particular renal and endocrine disorders (Whelton et al., 2018; Young et al., 2017). The syndromes of mineralocorticoid excess (SME) describe a heterogeneous group of clinical manifestations that lead to endocrine hypertension, typically either directly through activation of mineralocorticoid receptors (MR) and indirectly by disruption of pre-receptor regulation or through disturbed renal sodium homeostasis (Beck et al., 2020b; Carvajal et al., 2020). SME can be genetically determined or due to exposures to environmental factors such as certain nutrients or drugs, and the phenotypes can vary from severe to mild. Whilst genetic causes to SME have been extensively studied, less is known on the contribution of environmental factors that are expected to lead to milder phenotypes, which may often be unrecognized. The following sections cover the targets and mechanisms involved in SME, followed by a discussion of recent findings on azole antifungals causing acquired SME.

2. Targets of mineralocorticoid excess and underlying mechanisms

The MR is characterized by considerable substrate promiscuity and its activity is modulated by different classes of steroid hormones, *i.e.* mineralocorticoids (aldosterone, 11-deoxycorticosterone (DOC)), glucocorticoids (cortisol, corticosterone) and progestins (progesterone, 11β-hydroxyprogesterone) (Baker et al., 2017; Lathe et al., 2014). An excessive stimulation of MR leading to enhanced renal sodium reabsorption and resulting in water retention and volume expansion can be found in patients with primary aldosteronism (Gordon, 1994), (acquired) apparent mineralocorticoid excess (AME) (Ferrari, 2010), 11β- and 17α-hydroxylase deficiencies (Melcescu et al., 2012), Cushing's syndrome (CS) (Barbot et al., 2019), glucocorticoid resistance (Chrousos syndrome) (Charmandari et al., 2008), or MR activating mutations (Geller syndrome) (Geller et al., 1998). Increased sodium retention as a result of altered expression and activity of specific renal transporters and ion channels can be identified in Liddle syndrome or

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Abbreviations

11β-HSD2	11β-hydroxysteroid dehydrogenase type 2
ACTH	adrenocorticotropic hormone
AME	apparent mineralocorticoid excess
BCRP	breast cancer resistance protein
BP	blood pressure
BSEP	bile salt export pump
CS	Cushing's syndrome
CYP	cytochrome P450
DOC	11-deoxycorticosterone
GR	glucocorticoid receptor
HPA	hypothalamus-pituitary-adrenal
MDR	multidrug resistance
MIC	minimum inhibitory concentrations
MR	mineralocorticoid receptor
OATP	organic anion transporting polypeptides
OCT	organic cation transporter
OHI	hydroxy-itraconazole
P-glycoprotein	P-gp
PK	pharmacokinetics
SME	syndromes of mineralocorticoid excess
TDM	therapeutic drug monitoring
THF/THE	tetrahydrocortisol/tetrahydrocortisone
UGT	UDP-glucuronyl-transferase

pseudohyperaldosteronism type 2 (Gordon syndrome) (Athimulam et al., 2019; Hassan-Smith et al., 2011; Melcescu et al., 2012; Monticone et al., 2018). The phenotypes of all these disorders may be caused by inherited gene variants, somatic mutations or exposures to exogenous substances. Common biochemical findings in patients with SME are hypokalemia and low plasma renin activity, which is why these conditions are often also classified as low-renin hypertension.

Accumulating evidence proposes primary aldosteronism as the most commonly occurring form of SME (Funder et al., 2016; Perez-Rivas et al., 2019). A recent review reports that primary aldosteronism may account for up to 50% of all cases of high blood pressure diagnosed as essential hypertension (Funder, 2019). In normal physiology, adrenal aldosterone secretion is tightly controlled by the renin-angiotensin system. However, the excessive and mostly renin-angiotensin-independent secretion of aldosterone results in BP elevation, increased potassium excretion, and over time to a higher risk of renal and metabolic complications, stroke, and cardiovascular mortality compared to patients with essential hypertension. Most cases of primary aldosteronism occur sporadically or as inheritable forms, as reviewed elsewhere (Fernandes-Rosa et al., 2017; Monticone et al., 2018; Perez-Rivas et al., 2019).

Cortisol displays a similar binding affinity to the MR as aldosterone, although physiologically circulating aldosterone levels are two to three orders of magnitude lower than those of cortisol (Arriza et al., 1987; Edwards et al., 1988). In mineralocorticoid target tissues, the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) catalyzes the inactivation of cortisol to cortisone and protects the MR from the excessive amounts of cortisol, thereby rendering specificity for aldosterone (Funder et al., 1988). Mutations in this enzyme can cause the rare autosomal recessive disorder AME, characterized by hypertension, hypokalemia, as well as suppressed renin and aldosterone levels, (Mune et al., 1995; New et al., 1977; Wilson et al., 1995; Wilson et al., 1995, 1995). Distinct mutations can result in either a severe or milder SME phenotype (Funder, 2017; Tapia-Castillo et al., 2019; Yau et al., 2017). Mutations disrupting substrate and cofactor binding, affecting structural stability or inducing an inactive 11β-HSD2 dimer, are associated with increased disease severity, whilst mutations indirectly disrupting substrate binding or affecting single intramolecular interactions usually cause a mild phenotype (Yau et al., 2017). A diminished 11β-HSD2 function may not only be the result of a hereditary process, but may also be acquired. Acquired AME can be caused by dietary consumption of inhibitors, with licorice and its active component glycyrrhetinic acid being the most prominent example (Ferrari, 2010; Monder et al., 1989). Furthermore, as discussed in section 3.1, recent studies revealed that the therapeutic application of some azole antifungal drugs can provoke an acquired form of AME (Beck et al., 2020).

The metabolic inactivation of cortisol might not be sufficient to protect MR from activation by cortisol. Observations from cell-based enzyme activity measurements suggested that although 11β-HSD2 converts about 90% of supplied cortisol, the remaining cortisol is still present at about 10-fold excess over aldosterone, likely occupying the majority of MR (Funder, 2017). Based on this, Funder proposed a mechanism by which the NADH formed by 11β-HSD2 during the conversion of cortisol to cortisone prevents cortisol from activating the receptor. The high local levels of NADH, due to a close proximity of MR and 11β-HSD2 (Odermatt et al., 2001), might then ensure that cortisol-MR complexes remain inactive by allowing transcriptional co-repressors, such as the carboxyl-terminal binding protein (Fjeld et al., 2003), to serve as a metabolic sensors (Funder, 2017). Based on this hypothesis, both inhibition of 11β-HSD2 and redox changes occurring under conditions of oxidative stress or tissue damage can decrease NADH levels at the site of MR and result in cortisol-induced receptor activation.

Due to the pleiotropic effects of glucocorticoids, the pathophysiological mechanism for the development of hypertension secondary to glucocorticoid excess in CS is highly complex. One of the most frequently proposed mechanisms includes the inappropriate activation of MR by cortisol, potentially caused through substrate saturation of 11β-HSD2 (Stewart et al., 1995; Ulick et al., 1992). However, several studies indicate that the salt and water retention alone cannot explain the BP elevation (reviewed in (Baid et al., 2004; Barbot et al., 2019)). In this regard, synthetic glucocorticoids were shown to increase BP values, but without causing salt and water retention, suggesting an important role of the glucocorticoid receptor (GR) in the development of glucocorticoid-induced hypertension (Whitworth et al., 1989). Furthermore, only few CS patients display hypokalemia, a common biochemical finding in SME. This suggests that hypertension caused by hypercortisolism might be aggravated by mineralocorticoids but they may not be essential for its development.

Hypercortisolism is also associated with the syndrome of generalized glucocorticoid resistance, a rare, genetic condition characterized by target-tissue insensitivity to glucocorticoids, but without overt signs of CS (reviewed by (Charmandari et al., 2008; Vitellius et al., 2020)). This syndrome is mainly linked to loss-of-function mutations in the GR gene and leads to an increase of the adrenocorticotropic hormone (ACTH) and thus hypothalamus-pituitary-adrenal (HPA) axis activation and increased production of adrenal steroids. In contrast to CS, the circadian rhythm is maintained. Currently, 31 mutations in GR associated with glucocorticoid resistance have been described. The clinical phenotypes are highly variable, suggesting a broad spectrum of underlying pathophysiological mechanisms. Only about 50% of the affected patients suffer from hypertension and hypokalemia (Vitellius et al., 2018). Some patients with SME showed high plasma ACTH levels, indicating stimulation of the production of adrenal steroids with mineralocorticoid effects such as DOC, whereas others had normal plasma DOC concentrations but an elevated ratio of the renal metabolites tetrahydrocortisol/tetrahydrocortisone (THF/THE) in the urine, indicating a reduced renal inactivation of cortisol by 11β-HSD2 (Bouligand et al.,

2010; Chrousos et al., 1982; Vitellius et al., 2016). Charmandari et al. proposed that this broad spectrum may encompass variations in the ligand sensitivity and signaling pathways of GR and MR, the regulation or ligand availability by enzymes such as 11β-HSD2, or the presence of other (epi)genetic factors affecting tissue sensitivity towards glucocorticoids and mineralocorticoids (Charmandari et al., 2008).

A gain-of-function mutation (S810L) located in the binding pocket of the MR has been described in a family with severe early-onset hypertension along with low aldosterone levels that was markedly exacerbated in the affected women during pregnancy (Geller et al., 2000). This mutation caused a constitutive activation of the receptor and an altered ligand specificity, with progesterone and other steroids lacking a 21-hydroxyl turning from MR antagonists to potent agonists, explaining the aggravated hypertension during pregnancy. In addition, spironolactone, a widely used MR antagonist for the treatment of hypertension, paradoxically activated the MR in these patients.

Mutations in genes involved in cortisol production can lead to hypertensive forms of congenital adrenal hyperplasia (Miller and Auchus, 2011). The adrenal biosynthesis of cortisol and aldosterone requires a hydroxylation step at position 11 of the steroid backbone (for an overview of steroidogenesis see Fig. 1). Progesterone and androstenedione are also hydroxylated in β-position at carbon-11 (Bloem et al., 2013; Glass et al., 2020); however, the contribution of these metabolites on blood pressure regulation remains unclear and this will not be discussed further in this review. The hydroxylation reaction is performed by two different enzymes, cytochrome P450 (CYP) 11B1 (also known as 11β-hydroxylase) and CYP11B2 (aldosterone synthase). CYP11B1 forms cortisol from 11-deoxycortisol and its diminished activity results in a pronounced stimulation of adrenal steroidogenesis through positive feedback via the HPA axis, thereby leading to typically increased 11-deoxycortisol and DOC levels. CYP11B2 catalyzes the reaction from DOC via the intermediates corticosterone and 18-hydroxycorticosterone to aldosterone (Strushkevich et al., 2013). Loss-of-function mutations of CYP11B2 result in abolished aldosterone levels along with salt wasting and hypotension (Globerman et al., 1988; White et al., 1992). The concentrations of the precursor DOC are elevated in these patients (Eugen Melcescu, 2013; Miller and Auchus, 2011). However, compared to aldosterone, DOC displays only moderate mineralocorticoid activity *in vivo*, explained by the lower receptor binding affinity (Sutanto et al., 1989) and stronger plasma protein binding ability of DOC (~6% of DOC is freely available, whereas >30% of aldosterone is unbound) (Zipser et al., 1980). Nevertheless, very high DOC levels, as seen in CYP11B1 deficiency, can cause excessive MR activation with hypertension and hypokalemia (Miller and Auchus, 2011). Elevated DOC levels due to the inability to produce cortisol are also observed in patients with deficient 17α-hydroxylase (CYP17A1) activity. The lack of 17α-hydroxylation activity leads to an over production of DOC and aldosterone, promoting hypertension and hypokalemia.

Indirect mineralocorticoid activity as a result of altered renal salt homeostasis has been described in patients with mutations in the renal epithelial sodium channel (ENaC) (Liddle syndrome) or in proteins regulating the expression of the renal Na^+/Cl^- cotransporter (pseudohyperaldosteronism type 2 or Gordon syndrome). While SME is generally associated with hypokalemia, patients suffering from pseudohyperaldosteronism type 2 have elevated serum potassium levels (reviewed by (Athimulam et al., 2019; Hassan-Smith et al., 2011; Melcescu et al., 2012; Monticone et al., 2018)).

This review focuses on conditions that are a result of interferences of azole antifungals with several pathways described above.

3. Systemically applied azole antifungals

Due to their potent and broad-spectrum antifungal activity the class of azole antifungals is one of the most widely applied first-line recommendations for the prophylaxis and treatment of many invasive fungal infections. Older imidazole derivatives such as clotrimazole, miconazole and ketoconazole are mainly used to treat superficial mycoses (Allen et al., 2015). In response, triazole antifungals including itraconazole, fluconazole, voriconazole, posaconazole and isavuconazole were developed to meet the need for systemic applications (for structures see Fig. 2A). Azole antifungals disrupt the integrity of the fungal cell membrane by inhibiting the fungal enzyme lanosterol 14α-demethylase (CYP51), leading to a reduced ergosterol biosynthesis and accumulation of toxic sterol precursors (reviewed by (Campoy et al., 2017; Gintjee et al., 2020; Wiederhold, 2018)). However, they are not fully selective and besides targeting fungal CYP51 they can also interfere with mammalian CYP enzymes, posing a risk for causing adverse off-target effects and serious drug-drug interactions. In the following sections, we will focus on azole antifungals causing mineralocorticoid excess.

3.1. Case reports

Several recent case reports raised evidence for an interference with adrenal steroidogenesis by inhibition of CYP11B1 under therapy with posaconazole (Agarwal et al., 2020; Barton et al., 2018; Boughton et al., 2018; Parker et al., 2020; Thompson et al., 2017, 2019; Wassermann et al., 2018). The studies described symptoms of SME, including hypertension, hypokalemia, low serum levels of aldosterone and renin, but elevated serum 11-deoxycortisol, a marker for inhibition of CYP11B1 (Table 1). However, the degree of the 11-deoxycortisol elevation showed a high variability between the cases, ranging from unchanged (Thompson et al., 2020) or weakly increased (1.1 times the normal range

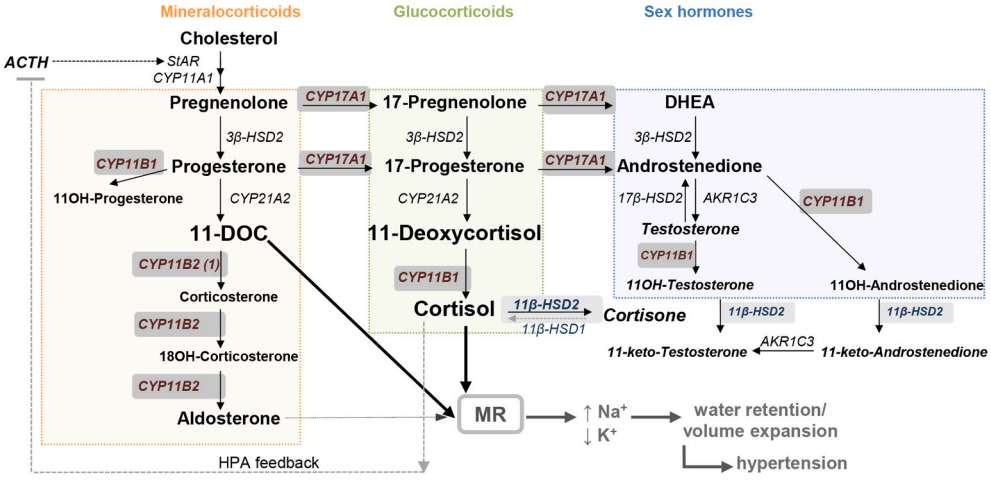

Fig. 1. Simplified overview of adrenal steroidogenesis. The mineralocorticoid 11-deoxycorticosterone (11-DOC) and the glucocorticoid 11-deoxycortisol that are elevated upon inhibition of CYP11B1 and CYP11B2 as well as the glucocorticoids cortisol and cortisone that are altered by inhibition of 11β-HSD2 are indicated by a slightly larger font. Steroids dependent on adrenal production but formed in peripheral tissues such as testosterone and its 11-oxy-metabolites are depicted in *italic*. The enzymes AKR1C3, 17β-HSD2 and 11β-HSD2 are not expressed in the adrenals at substantial levels.

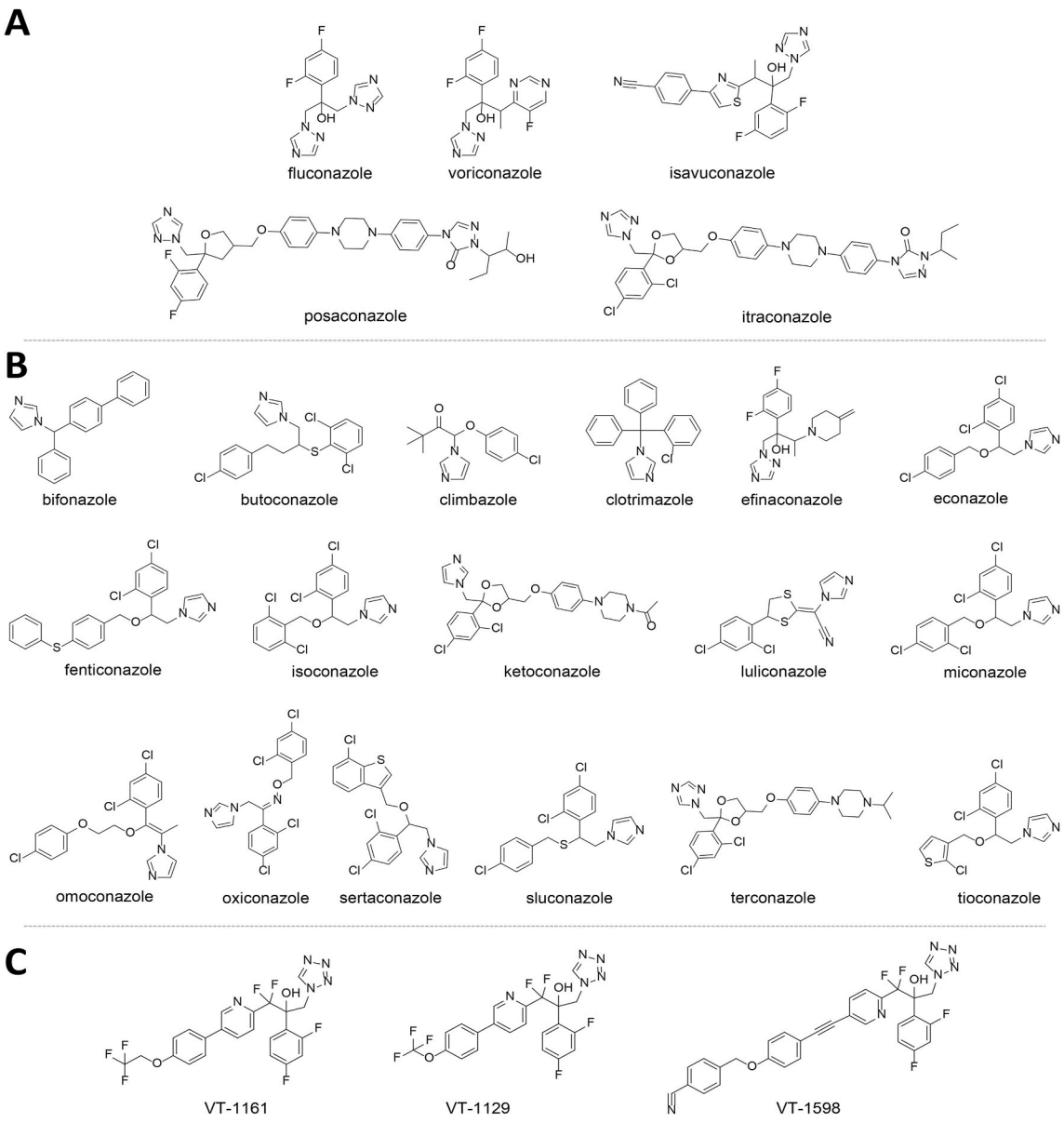

Fig. 2. Structural representation of azole antifungals. A) Systemically applied azole antifungals, B) topically administered azole antifungals and C) tetrazole antifungals in development.

limit (Thompson et al., 2017)) up to 15-22-fold the upper limit of the normal range (Agarwal et al., 2020; Barton et al., 2018; Boughton et al., 2018). Three of these patients additionally showed 10- to 20-fold increases in serum DOC levels (Barton et al., 2018; Boughton et al., 2018) and 70-fold elevated DOC levels on a standard synacthen test (Agarwal et al., 2020), respectively; however, in other patients DOC was within the normal range (Parker et al., 2020; Thompson et al., 2017, 2019). It needs to be noted that ideally several measurements of endocrine hormones should be made to verify the involvement of a specific enzyme; however, in clinical practice this is often not feasible. Furthermore, serum levels do often not reflect intra-tissue concentrations and regarding MR-dependent hypertension and hypokalemia the respective steroid concentrations mainly in the kidney are relevant. Nevertheless, these observations suggest that besides inhibition of CYP11B1 other mechanisms are involved in the posaconazole-induced SME. The low aldosterone levels observed in these patients can be explained by a simultaneous inhibition of CYP11B1 and CYP11B2, with a more pronounced effect towards CYP11B2. A selective inhibition of CYP11B2, however, would be expected to show normal cortisol production (therefore also normal 11-deoxycortisol) but a lack of aldosterone, resulting in hypokalemia and hypotension (Azizi et al., 2013). Despite the indications from *in vitro* experiments on a potent inhibition of the 17, 20-lyase reaction (Yates et al., 2017), the effect of posaconazole on CYP17A1 remains unclear since 17α-hydroxyprogesterone (indicating 17α-hydroxylase activity) was either normal or slightly elevated (Barton et al., 2018; Thompson et al., 2017, 2019) and androstenedione and testosterone (requiring 17,20-lyase activity) were either decreased (Thompson et al., 2019), unchanged (Thompson et al., 2020) or slightly elevated (Barton et al., 2018; Boughton et al., 2018).

In some of these case reports the serum cortisol/cortisone ratio was also examined and in five out of seven cases elevated values were found (1.3–3.3-fold the upper range) (Agarwal et al., 2020; Boughton et al., 2018; Thompson et al., 2017, 2019, 2020; Wassermann et al., 2018), which were mostly due to decreased cortisone concentrations. An increased cortisol/cortisone ratio (particularly of urinary free cortisol/cortisone) gives evidence for a reduced 11β-HSD2 activity, with typically decreased cortisone values. The inhibition of 11β-HSD2 by itraconazole and posaconazole has been studied *in vitro* (Beck et al.,

Table 1
Summary of SME case reports after application of itraconazole or posaconazole.

	Reference range	Denolle et al. (2014)	Hoffmann et al. (2018)		Thompson et al. (2017)			Thompson et al. (2019)					Mahmood et al. (2017)		
Age/sex treatment		68 y, m Itraconazole	59 y, m Itraconazole	change to voriconazole	67 y, m Posaconazole			54 y, m Posaconazole		73 y, m Posaconazole			44 y, m Posaconazole		
dose [mg/day]		200	2 × 300	2 × 200	300 (after 35 days)	21 days withhold of posa. therapy	100 (after 4 weeks of therapy)	300	300 (4 weeks later)	300 (after 9 weeks of therapy)	200 (after 4 weeks of therapy)	100 (after 3 weeks of therapy)	300 (2 weeks after initiation)	200 (after 2 months)	100
Serum azole [ng/mL]	posa: >700-1000 itra: >500-1000	2827	2180 (OHI 3750)	na	4360	na	1240	3100	2700	5000	3300	1680	7980	5180	2160
BP systolic/ diastolic [mm Hg]	90-120/60-80	164/90	150-188/70-97	"normal"	165/89	"normal"	115/63	163/94	na	154/69	na	130/76	na	154/98	"normal"
Serum K^+ [mmol/L]	3.5–5.0	2.5–3.5	3.8 (4.3 before therapy)	"normal"	3.4	"normal"		3.1	na	3.3	na	4.4	na	2.2	"normal"
ACTH [pg/mL]	6.0–76	"normal"	na		47	na		na		na			na		
Renin [pg/mL]	30–40	6						0.2	na				na	<700	na
Renin activity [ng/mL/h]	0.25–5.8		0.13	0.69	0.11	1.34	2.47			0.36	0.1	na			
Aldosterone [ng/dL]	2.0–45 (supine or upright)	1.0	<1	4	<1	4	3	<3	<3	<2	<2	na	na	<4.0	na
Cortisol (F) [µg/dL]	5-25 (8am–12am) 5-15 (12am-8pm)	"normal"	11.2	13.5	14.6	na		na	7.4	na	5.2	na	na	17 (early morning)	na
Cortisone (E) [µg/dL]	1.2–3.5	na	na		1.4	na		na	1.65	na	0.19	na	na		
F/E ratio	2–8	na	na		10.4	na		na	4.5	na	27	na	na		
DOC [ng/dL]	2.0–19	"normal"	<16	na	2	na		na	8,3	na	3,2	na	na		
11-deoxycortisol [ng/dL]	12-158 (8am)	na	55	na	177	36	<20	320	216	406	186	na	na		
Testosterone (total) [ng/dL]	270-1070 (male) 6-86 (female)	na	na		36.9 (free)	na		na	242	na	32	na	na		
Androstenedione [ng/dL]	50–250	na	na		na			na	46	na	3.8	na	na		
17OH-Progesterone [ng/dL]	5-250 (male) 20-500 (premenopause) ≤70 (postmenopause)	na	na		129	na		na	102	na	36	na	na		
Estradiol [pg/mL]	<20 (male) <20–443 (premenopause) <59 (postmenopause)	na	40	26	48	35	26	49	na	15	<15	na	na		
summary antifungal therapy		stopped itraconazole treatment	1. fluconazole (normal BP 110–134/62-70 mmg Hg and normal serum K+ 4.3 mM, but severe dry skin– > stopped 2.itraconazole– > stopped 3. voriconazole (symptoms resolved)		1. voriconazole (visual hallucinations) 2. isavuconazole 3. posaconazole– > dose de-escalation			1. fluconazole (nausea, cheilitis and xerosis)– > stopped 2. posaconazole– > stopped 3. isavuconazole (symptoms resolved)		1. liposomal amphotericin B 2. posaconazole			1. itraoconazole (pruritus and urticaria after 5 days)–> stopped 2. posaconazole– > dose de-escalation		

	Reference range	Martino et al. (2015)	Barton et al. (2018)		Boughton et al. (2018)	Kuriakose et al. (2018)	Wassermann et al. (2018)			Parker et al. (2020)			Dipippo and Kontoyiannis (2020)		
Age/sex treatment		13 y, f Posaconazole	15 y, m Posaco-nazole	3 weeks after stopping posaconazole	67 y, m Posaconazole	>60 y, f Posaconazole	67 y, f Posaconazole			12 y, f Posaconazole			68 y, f before therapy	Posaco-nazole	Isavuco-nazole
dose [mg/day]		400 mg suspension for 3 days, inadvertently followed by 400 mg delayed release tablets	na	na	200	300	300	200	100	300 (for 12 days)	400	dis-contiuation	na	300	na
Serum azole [ng/mL]	posaconazole: >700-1000 itraconazole: >500-1000	9500	3000	na	na	4900 after 2 weeks; 6100 after 4 month	3970	3270	2380	1660	2490	na	na	6380	na
BP systolic/ diastolic [mm Hg]	90-120/60-80	no BP elevation described	176/72	102/64	150-170/na	179/86	na	"normal"	na	already hypertensive before, no amelioration			102-135/58-84	147-197/77-98	112-150/58-90
Serum K^+ [mmol/L]	3.5–5.0	2.7	2.8	4.3	2.7–2.9	2.9	na	2.8	3.2–4.4 (with K+ supplement	3.6 (decline of 0.5 during therapy)		na	4.1–4.8	3.5–3.7	4.7
ACTH [pg/mL]	6.0–76	na	na		118	na	na			na			na		
Renin [pg/mL]	30–40	na			<0.3	<3							na		
Renin activity [ng/mL/h]	0.25–5.8	na	1.2	na			na	<0.6	na	na	0.6	na			
Aldosterone [ng/dL]	2.0–45 (supine or upright)		<0.4	na	1.2	<2	na	<4.0	na	na	<3	na	na		
Cortisol (F) [μg/dL]	5-25 (8am–12am) 5-15 (12am-8pm)	na	13	17	8.2	11.3	na			na	13.4	na	na		
Cortisone (E) [μg/dL]	1.2–3.5	na	na		0.53	na	na			na			na		
F/E ratio	2–8	na	na		15.3	na	na	na	16.1	na			na		
DOC [ng/dL]	2.0–19	na	247	24	413	na	na			5 (before therapy)	18	<5	na		
11-deoxycortisol [ng/dL]	12-158 (8am)	na	2445	167	2186	na	na	na	519	na	206.5	26.6	na		
Testosterone (total) [ng/dL]	270-1070 (male) 6-86 (female)	na	na		na	na	na			na			na		
Androstenedione [ng/dL]	50–250	na	194	75	261	na	na			na			na		
17OH-Progesterone [ng/dL]	5-250 (male) 20-500 (premenopause) ≤70 (postmenopause)	na	452	215	na	na	na			na			na		
Estradiol [pg/mL]	<20 (male) <20–443 (premenopause) <59 (postmenopause)	na	na		na	na	na			na			na		
summary antifungal therapy		1. liposomal amphotericine B and voriconazole 2. posaconazole	stopped posaconazole		stopped posaconazole and added Spironolactone and oral K+	1. Itraconazole (hives)– > stopped 2. voriconazole (alopecia)–> stopped 3. posaconazole 4. fluconazole				1. isavuconazole– > stopped 2. posaconazole– > stopped			1. voriconazole– > stopped 2. posaconazole– > stopped 3. isavuconazole		

	Reference range	Pandit et al. (2020)	Agarwal et al. (2020)		Thompson et al. (2020)		
Age/sex		68 y, f	6 y, m		38, m		
treatment		Posaconazole	Posaconazole	3 weeks after stopping posaconazole	fluconazole	Posaconazole delayed release tablets	voriconazole
dose [mg/day]		300	300	na	600	300	2 × 200
Serum azole [ng/mL]	posaconazole: >700-1000 itraconazole: >500-1000	na	6000	na	na	2640	na
BP systolic/diastolic [mm Hg]	90-120/60-80	120-130 before posaconazole and on hypertensive therapy 160–170 on posaconazole and hypertensive treatment	150/84	92/56	"normal"	155/98	"normal"
Serum K^+ [mmol/L]	3.5–5.0	2.6	4.3	na	"normal"	"hypokalemia"	"normal"
ACTH [pg/mL]	6.0–76	na	13.6	na	na	na	na
Renin [pg/mL]	30–40		1	na			
Renin activity [ng/mL/h]	0.25–5.8	0.05			na	0.6	"normal"
Aldosterone [ng/dL]	2.0–45 (supine or upright)	2.0	1.6	na	na	<1	31
Cortisol (F) [μg/dL]	5-25 (8am–12am) 5-15 (12am-8pm)	na	15.2[a]	26.5[a]	na	11.1	na
Cortisone (E) [μg/dL]	1.2–3.5	na	1.5[a]	2.0[a]	na	1.8	na
F/E ratio	2–8	na	12	3.5	na	6.2	na
DOC [ng/dL]	2.0–19	na	1355[a]	53[a]	na	na	na
11-deoxycortisol [ng/dL]	12-158 (8am)	na	3534[a]	173[a]	na	40	na
Testosterone (total) [ng/dL]	270-1070 (male) 6-86 (female)	na	Na		na	631	na
Androstenedione [ng/dL]	50–250	na	Na		na	na	na
17OH-Progesterone [ng/dL]	5-250 (male) 20-500 (premenopause) ≤70 (postmenopause)	na	3534[a]	173[a]	na	na	na
Estradiol [pg/mL]	<20 (male) <20–443 (premenopause) <59 (postmenopause)	na	Na		na	63	22
Summary antifungal therapy		Dose reduction of posaconazole to 100 mg/day and added Spironolactone	stopped posaconazole treatment[a] on Standard synacthen test		1. fluconazole– > stopped 2. posaconazole– > stopped 3. voriconazole		

2017); revealing IC_{50} values for itraconazole and its major pharmacologically active metabolite hydroxy-itraconazole (OHI) in the lower nanomolar range and a more moderate but still nanomolar inhibition by posaconazole.

Two case studies reported a manifestation of SME following itraconazole treatment (Denolle et al., 2014; Hoffmann et al., 2018). Both patients showed hypertension, hypokalemia and low renin and aldosterone levels, but unremarkable concentrations of cortisol and DOC, best resembling an acquired form of AME. The findings of these case reports are supported by phase II studies assessing the antitumor efficacy of itraconazole in prostate cancer patients. Antonarakis et al. observed the same combination of adverse effects comprising hypertension and hypokalemia with a dose-dependent incidence in patients with metastatic castration-resistant prostate cancer (Antonarakis et al., 2013). Additionally, edema was a most frequently observed adverse effect. In fact, 34.5%, 31% and 17.2% of the 29 patients in the high dose itraconazole treatment group (600 mg/day) developed edema, hypertension and hypokalemia, respectively, whereas 23.5% of 17 patients in the low dose group (200 mg/day) developed edema but none of them hypertension and hypokalemia. Moreover, the high dose group showed suppressed serum aldosterone concentrations along with increased plasma ACTH but unaffected serum cortisol. Based on this study, the authors treated a single patient with biochemically recurrent prostate cancer with 600 mg itraconazole daily (Suzman et al., 2014). During the 5 months' treatment period, the patient developed hypoaldosteronism, with an elevation of ACTH, cortisol and DHEA concentrations, although still in the normal range. Over all, the patient responded with only minimal adverse events; however, potassium levels and blood pressure were unfortunately not assessed. Another phase II study including 21 patients suffering from biochemically recurrent prostate cancer and receiving 600 mg itraconazole per day reported edema (52%), hypertension (24%) and hypokalemia (24%) as the most common adverse effects during a median treatment duration of 4 months (Lee et al., 2019). Furthermore, a recent retrospective, single-center case study analyzed the medical records of patients treated with itraconazole and developing cardiac toxicity, between 1999 and 2019 (Teaford et al., 2020). Among the 31 patients included, the most common symptom was edema (74%). New onset hypertension or worsening of an existing hypertension was found in 26% of the patients. Unfortunately, in the above mentioned studies further steroid hormones that could have provided mechanistic information such as DOC, 11-deoxycortisol and cortisone were not included in the measurements.

3.2. Mechanistic evaluation

Sharkey et al. proposed a distinct mechanism for the itraconazole-dependent interference with the endocrine system compared to ketoconazole, with a greater potency to inhibit CYP11B1 (Sharkey et al., 1991). Nevertheless, only recently an *in vitro* study employed enzyme activity measurements using recombinant proteins as well as molecular modeling to address the underlying molecular mechanisms by which posaconazole and itraconazole can lead to SME (Beck et al., 2020). Both azole antifungals potently inhibited CYP11B1 and CYP11B2 (low nanomolar IC_{50} values) with a preference of both compounds for CYP11B2 and a 7-fold greater inhibition of CYP11B1 by posaconazole over itraconazole. OHI was significantly less active against both enzymes. Furthermore, posaconazole and itraconazole neither inhibited the 17α-hydroxylase activity of CYP17A1 nor directly activated the MR. These results on posaconazole are in line with an earlier study showing potent inhibition of CYP11B1 and CYP11B2 by posaconazole with IC_{50} values in the lower nanomolar range (Yates et al., 2017). In addition, this latter study detected a weak inhibition of the 17α-hydroxylase activity by posaconazole while the 17,20-lyase reaction was greatly inhibited. Not all of the analyzed cases displayed elevated 11-deoxycortisol and DOC, the markers for CYP11B1 inhibition, and in some patients the inhibition of 11β-HSD2 may be the predominant mechanism causing SME. 11β-HSD2 inhibition may be more relevant for itraconazole than posaconazole as its potency is about three times higher (Beck et al., 2017). The concentrations that these two drugs can reach in the adrenal glands and in the kidneys, however, remain unknown, and effects on 11β-HSD2 cannot be extrapolated from rodent studies due to significant species differences. Nevertheless, the mode-of-action proposed in the case studies described above could be mechanistically supported.

The above mentioned cases raised the question whether the symptoms of SME represent a class effect of triazoles or are limited to the structurally similar compounds itraconazole and posaconazole (Dipippo and Kontoyiannis, 2020) (for structures see Fig. 2). Importantly, substitution of posaconazole or itraconazole therapy by voriconazole, fluconazole or isavuconazole led to the resolution of the mineralocorticoid excess symptoms in several of the reported cases (Dipippo and Kontoyiannis, 2020; Hoffmann et al., 2018; Kuriakose et al., 2018; Martino et al., 2015; Parker et al., 2020; Thompson et al., 2017, 2019), and no signs of SME were observed if the antifungal therapy preceding the administration of itraconazole or posaconazole was based on voriconazole, fluconazole or isavuconazole. Therefore, overt inhibition of CYP11B1, CYP11B2 and 11β-HSD2 by other systemically applied azole antifungals including voriconazole, fluconazole and isavuconazole is highly unlikely. This was supported recently by *in vitro* data showing very weak inhibitory activities against these enzymes (IC_{50} values $\gg 1$ μM) (Beck et al., 2020a). An exception is the imidazole ketoconazole, already known since the 1980s for its inhibition of CYP11B1 and CYP17A1 and the resulting mineralocorticoid phenotype (Aabo et al., 1987). However, with a few exceptions for a systemic therapy, *i.e.* in CS, ketoconazole is only applied topically (Beck et al., 2020b).

The extended hydrophobic central region of posaconazole, itraconazole and ketoconazole seems to drive the inhibitory effect towards CYP11B1/2 and 11β-HSD2. For the latter enzyme, a clear structure-activity-relationship could be identified: the larger the azole scaffold size, the more potent its inhibitory activity towards 11β-HSD2 and the higher the selectivity over the closely related 11β-HSD1 (Beck et al., 2017). Docking studies using a homology model of 11β-HSD2 predicted a hydrogen bond interaction of the potent inhibitors itraconazole and OHI with the catalytic residue Tyr232 as well as an aromatic contact with Arg279 (Beck et al., 2020). Of note, itraconazole and OHI did not entirely fit into the binding site of the enzyme, but aligned at the surface of the protein. Due to the lack of considerable similarity with other short-chain dehydrogenases and the high flexibility of the C-terminal region, crystal structures with the respective inhibitors are ultimately needed to elucidate the relevant ligand-protein interactions. Nevertheless, patients with a mutation in the catalytic Tyr232 obviously suffer from a severe AME phenotype, while a mutation of Arg279 to cysteine has been reported to cause a mild form of AME (Yau et al., 2017). Arg279, which is closely located to the surface of the protein, was proposed to form a hydrogen bond with the backbone of Asn171, helping to stabilize the local protein environment. Asn171 was predicted previously to stabilize the binding of substrates (Furstenberger et al., 2012) and to interact with the cofactor (Arnold et al., 2003). A disruption of such an intramolecular interaction, which could be caused not only by a genetic mutation but possibly also by an interaction with a xenobiotic such as itraconazole, might disturb the arrangement of the local protein structure, ultimately resulting in reduced enzyme activity.

Interestingly, three novel tetrazole antifungals, VT-1129, VT-1598 and VT-1161, are currently in different developmental stages (preclinical phase, phase II and phase III, respectively) (Nishimoto et al., 2019; Nishimoto et al., 2019; Wiederhold, 2018; Yates et al., 2017). These tetrazole antifungals were designed to be more specific towards fungal CYP51 and have less undesired interactions with human CYP enzymes because of less pronounced interactions with the heme group, therefore possessing a better safety profile. Indeed, in contrast to posaconazole and itraconazole, the tetrazole compounds did neither inhibit CYP3A4, the major human CYP responsible for drug-drug interactions, nor CYP2C9 and CYP2C19 (Warrilow et al., 2014; Yates et al., 2017).

These tetrazole compounds share some structural similarity with ketoconazole (Fig. 2) and thus besides drug metabolizing CYPs, enzymes involved in steroidogenesis might be potential targets for side-effects. At present, limited data is available for a potential inhibition by these tetrazoles of steroidogenic CYPs (CYP11A1, CYP11B1/2, CYP17A1, CYP21A2, CYP19A1) or enzymes involved in peripheral steroid metabolism including 3β-HSDs, 11β-HSD1/2 and 17β-HSDs. However, VT-1598 was reported to be inactive towards CYP11B1/2, CYP17A1 and CYP19A1, in contrast to posaconazole (Yates et al., 2017). Thus, the tetrazoles seem to exhibit much higher selectivity for fungal CYP51 over human CYPs. It will be interesting to see whether these tetrazoles are also inactive towards short-chain dehydrogenases such as 11β-HSD2, especially VT-1598 bearing the extended hydrophobic part. Until such information is available, patients treated with tetrazoles may be monitored for signs of SME.

3.3. Drug serum concentrations

The majority of the itraconazole- and posaconazole-dependent SME cases reported above received the standard daily dosage of 200 mg itraconazole and 300 mg posaconazole, respectively. However, one patient received twice daily 300 mg itraconazole (Hoffmann et al., 2018), one patient was given 200 mg posaconazole per day (Boughton et al., 2018) and another patient was inadvertently prescribed with 400 mg/day of the posaconazole delayed-release tablet outpatient application after 3 days of inpatient treatment with 400 mg of the suspension solution (Martino et al., 2015) (Table 1). Regarding posaconazole, the drug formulations are not interchangeable, due to significant differences in pharmacokinetics (PK). Importantly, all reported cases exhibited a serum concentration of posaconazole or itraconazole that was exceeding the targeted therapeutic range, and in five of the cases a dose-de-escalation resulted in the resolution of the mineralocorticoid excess phenotype. A retrospective analysis of twenty patients diagnosed with posaconazole-induced pseudohyperaldosteronism revealed that the most common therapeutic modification was posaconazole dose reduction, followed by drug discontinuation, change to an alternative antifungal and additional treatment with spironolactone (Davis et al., 2020). A dose-dependent incidence of mineralocorticoid symptoms was also reported in the earlier mentioned itraconazole phase II study in prostate cancer patients (Antonarakis et al., 2013) and the retrospective, single-center case study, analyzing itraconazole-mediated cardiac toxicity over the past twenty years (Teaford et al., 2020). In order to assess the incidence of mineralocorticoid excess symptoms and their association with serum posaconazole drug levels, a single-center, retrospective, observational study evaluated differences in serum posaconazole concentrations and clinical characteristics in outpatients newly starting posaconazole therapy (Nguyen et al., 2020). Significantly higher serum posaconazole concentrations were found in patients with mineralocorticoid excess symptoms compared to patients without these adverse effects (3000 *vs* 1200 mg/mL). Furthermore, serum posaconazole concentrations positively correlated with systolic BP changes and with serum 11-deoxycortisol levels but negatively correlated with serum potassium levels. A study in patients receiving 300 mg posaconazole once daily as tablets for treatment or prophylactic purposes showed mean steady-state serum trough concentrations of posaconazole of 1720 ng/mL, with the majority (52%) of patients exhibiting concentrations between 1250 and 2500 ng/mL (Cornely et al., 2016). 10% of the patients achieved serum trough concentrations between 2500 ng/mL and 3750 ng/mL and 3% > 3750 ng/mL up to 9140 ng/mL. Hypokalemia was detected in 22% of all patients, however, the occurrence of hypertension was not reported. Moreover, no correlation was found between posaconazole plasma exposures and the incidence of adverse events. The same authors investigated PK and safety of an intravenous posaconazole formulation (Cornely et al., 2017). Mean steady-state through concentrations after 300 mg of posaconazole *iv* once daily was 1090 ng/mL (range 295–2485 ng/mL). Most patients (94%) had an average serum steady-state exposure of 500–2500 ng/mL and only 6% of the patients exhibited >2500 ng/mL up to 3650 ng/mL. The most commonly experienced adverse events were diarrhea (32%), hypokalemia (22%) and pyrexia (21%), and only 1% of the patients developed hypertension (moderate, n = 1; severe, n = 2). A correlation between drug serum concentrations and adverse events was not investigated. Earlier clinical trial results revealed an incidence of hypokalemia and hypertension of 22% and 11% in patients receiving 300 mg daily oral posaconazole, whereby hypokalemia was mainly attributed to the vomiting and diarrhea (MSD-MERCK-SHARP&DOHME-AG, 2014). To assess the safety of a high-dose posaconazole therapy, Schauwvlieghe et al. recently examined a group of patients treated with a median posaconazole dose of 600 mg/day to achieve posaconazole serum trough concentrations of >3000 ng/mL (Schauwvlieghe et al., 2020). Most patients (13) received posaconazole tablets, 1 patient an oral suspension solution and 2 patients a combination of both formulations. Six out of 16 patients showed trough concentrations between 3000 and 4000 ng/mL and 10 patients >4000 ng/mL. Hypokalemia was the most commonly reported adverse event, whereby the treatment of three patients was discontinued due to the development of arterial hypertension. Additionally, they examined a second group of patients in whom a median serum trough concentration of 4300 ng/mL was reached with application of the licensed dose (tablets and *iv* solution: 300 mg/day; oral suspension: 800 mg/day). A total of 32% of the patients developed hypokalemia and 16% hypertension. Furthermore, as a most striking case they described a patient who developed several hypertensive crises and hypokalemia with undetectable levels of aldosterone but normal renin concentrations. Although serum trough concentrations >3000 ng/mL were achieved in all cases in that study, regardless of the dosage regime, the total incidence of hypokalemia was about 34% and that of hypertension 17%. In this regard, Nguyen et al. recently found that 37.5% of patients with serum posaconazole levels between 3000 and 3900 ng/mL and all with levels >4000 ng/mL met the definition of pseudohyperaldosteronism (Nguyen et al., 2020).

In a study of 47 patients receiving 100–400 mg itraconazole daily for the treatment of nonmeningeal coccidioidomycosis, 23 patients were classified as asymptomatic throughout the treatment and five patients developed edema, two hypertension and one hypokalemia (Graybill et al., 1990). Unfortunately, no correlation was drawn between the itraconazole dosage and the occurrence of adverse effects. A high-dose itraconazole treatment with 600 mg/day showed mean serum trough levels of >5000 ng/mL in a small study on eight patients with severe systemic mycoses (Sharkey et al., 1991). Two of these patients showed no improvement during treatment and the failures were associated with low itraconazole serum concentrations (<2500 ng/mL). The entire group of patients was significantly associated with hypokalemia during itraconazole treatment. One patient developed reversible adrenal insufficiency with normal urinary levels of 17-ketosteroids but low levels of free cortisol. In another patient, hypertension, mild edema and suppressed serum aldosterone concentrations (<2.5 ng/dL) were observed, whereas two other patients were noted with significantly increased BP values.

Administration of 800 mg itraconazole daily in a patient with cerebral aspergillosis resulted in a progressive increase of the serum itraconazole concentration up to 30 μg/mL over 5 month (Sanchez et al., 1995). Although the patient developed hypokalemia and edema, she seemed to tolerate the therapy well. A further case report included a patient with spondylodiscitis caused by an Aspergillus infection who received 900 mg/day itraconazole (Takagi et al., 2001). During itraconazole therapy, maximum serum itraconazole and OHI concentrations of 5924 ng/mL (day 19) and 13000 ng/mL (day 26), respectively, were reached. Interestingly, the authors did not describe any adverse events, suggesting that these high serum concentrations were achieved in the absence of overt adverse effects in this patient.

Despite the evidence for a dose-dependent incidence of mineralocorticoid excess symptoms during therapy with itraconazole and

posaconazole, there are currently no studies available defining an upper plasma target level that can be considered safe regarding these adverse effects. For the registration of the posaconazole tablet formulation by the European Medicines Agency (EMA), a provisional cutoff of 3750 ng/mL was applied by PK studies (Cornely et al., 2016; Ullmann et al., 2018). However, guidelines recommend only steady-state (>7 days after drug initiation) serum trough concentrations of >0.7 μg/mL for patients receiving posaconazole for prophylaxis and >1.0–1.25 μg/mL for patients with established infections (Ashbee et al., 2014; Dekkers et al., 2016; Howard et al., 2012; John et al., 2019; Ullmann et al., 2018). For itraconazole a serum trough concentration of >0.5–1 μg/mL as lower target level is recommended (Ashbee et al., 2014). In view of the mineralocorticoid excess symptoms associated with serum posaconazole and itraconazole concentrations ≥2.5–3 μg/mL, we propose the introduction of upper plasma target levels in combination with a therapeutic drug monitoring (TDM) strategy in order to prevent the occurrence of SME. Moreover, as observed, antifungal therapy with azoles is associated with significant interindividual differences, which further emphasizes the use of TDM (see below).

In this regard, no major side effects were observed in a palliative case where itraconazole as high as 1600 mg was applied daily, and the patient's condition improved unexpectedly over time (Palanisamy et al., 2005). Importantly, this drastic dose-escalation was performed because the therapeutic serum drug levels were not reached with standard itraconazole doses (400 mg/day). The patient achieved only serum peak levels of 80 ng/mL itraconazole and 70 ng/mL OHI with an *iv* application of 800 mg itraconazole. A change to oral administration of 800 mg itraconazole as capsules led to serum itraconazole concentrations of 500 ng/mL, and with a further increase to 1200 mg/day the patient reached peak levels of 1000 ng/mL. The authors proposed as possible explanations for the low serum concentrations of itraconazole a reduced oral absorption and/or an increased clearance of itraconazole through induction of hepatic CYP3A4.

3.4. Interindividual pharmacokinetic differences

The latter case stands in marked contrast to the high azole plasma concentrations found in patients with an SME phenotype. These considerable interindividual differences contributing to a lack of efficacy or adverse effects of azole antifungals may be explained at least in part by genetic polymorphisms influencing ADME properties and thus pharmacokinetics, and by additional factors affecting drug levels, including environmental and (patho-) physiological changes (Ashbee et al., 2012; Meletiadis et al., 2006).

Itraconazole and posaconazole are associated with a highly variable oral bioavailability, depending particularly on the drug formulation, gastric pH, concomitant food intake, but also gut motility and health status of the recipient. Two itraconazole drug formulations are available to date, an oral solution and capsules, whereby the oral solution displays an enhanced bioavailability (Barone et al., 1998; Dekkers et al., 2016; Dolton et al., 2014). In contrast to the oral solution, itraconazole capsules should be administered with food and in the presence of an acidic gastric environment to achieve maximal absorption (Van de Velde et al., 1996). SUBA (SUper-Bio-Available) itraconazole represents the latest capsule formulation consisting of a solid dispersion of itraconazole in a pH-dependent polymer matrix that improves dissolution and absorption and reduced interpatient variability when compared to conventional capsules (Abuhelwa et al., 2015; Tolsura, 2018).

Posaconazole can be found on the market as oral suspension, delayed-release tablets or as *iv* infusion solution. The use of the currently available oral posaconazole suspension solution is limited due to inter- and intraindividual pharmacokinetic differences caused by a saturable absorption and highly variable bioavailability (reviewed by (Li et al., 2010)). Higher and more consistent plasma levels can be achieved by the newer posaconazole delayed-release tablets, which are less susceptible to absorption variabilities (Ullmann et al., 2018; Wiederhold, 2016). Nevertheless, in a recent case report of a patient who had undergone terminal ileum resection, persistent subtherapeutic posaconazole trough levels were described despite the use of high-dose posaconazole delayed-release tablets (up to 600 mg/day) (Zhou et al., 2019). An important role of the more distal intestinal regions for posaconazole absorption has been suggested by a study exploring the intraluminal behavior and systemic exposure of posaconazole after intake of a delayed-release tablet (Hens et al., 2016).

Due to the slow drug accumulation, steady-state posaconazole and itraconazole concentrations are achieved within 7–15 days after initiation of therapy. The application of an initial loading dose allows to reach concentrations that are likely to be effective and safe within the first days of the treatment. Their lipophilic character leads to strong binding to plasma proteins (>98 and > 99%) and a large distribution volume with a tendency to penetrate into tissues bearing a high lipophilic content (Felton et al., 2014). Low albumin concentrations were found to be associated with subtherapeutic posaconazole trough levels (Maleki et al., 2018; Oh et al., 2020; Tang et al., 2017). Hypoalbuminemia can be the secondary consequence of increased gastrointestinal protein losses or malnutrition, which may reduce drug absorption, but can also be triggered by (patho-) physiological changes. Since only the unbound drug fraction of posaconazole can be metabolized and, in contrast to itraconazole, the metabolites are devoid of antimycotic efficacy, lower protein binding leads to increased metabolism and can cause an enhanced drug clearance, resulting in decreased total plasma posaconazole concentrations. In line, a recent study described an association of low serum albumin concentrations with a reduced probability of attaining target total but not unbound posaconazole concentrations (Sime et al., 2019). Structural changes of plasma proteins can also affect drug binding capacities und therefore the fraction of freely available drug; however, no data are available to date on whether this affects the PK of itraconazole or posaconazole (Kragh-Hansen et al., 1990).

Concerning the clinical SME phenotype induced by the inhibition of CYP11B1 and 11β-HSD2, the intra-tissue concentrations, *i.e.* in the adrenals and kidney/colon are critical. However, currently such data is mostly lacking in humans. In rats, *iv* administration of 10 mg/kg itraconazole yielded concentrations in the kidney of 5.5 μg/g 1 h after application, reaching three times the plasma concentration, and 5.9 μg/g after 24 h, which was 31 times the plasma concentration. Another study reported itraconazole concentrations in rat kidneys of 0.84 μg/g 4 h after *iv* application of 10 mg/kg itraconazole and 0.47 μg/g after 24 h (Van Cauteren et al., 1987). These concentrations corresponded to 5–9 times the concentrations in the plasma. In humans, a kidney concentration of 0.5 μg/g was described in a single patient, which was only 1.5 times the plasma concentration (reviewed by (Felton et al., 2014)). Posaconazole tissue concentrations were investigated in human autopsy specimens from seven patients, receiving posaconazole as prophylaxis (Blennow et al., 2014). Tissue concentrations in the heart, lung, liver and kidney exceeded plasma concentrations (10–390 ng/mL) in all patients, with highest levels in liver tissue (6- to 66-fold increase compared to plasma levels), followed by kidney (4- to 32-fold increase), heart (4- to 18-fold increase), and lung (2- to 20-fold increase). However, due to the variable dosage of posaconazole and the elapsed time between drug intake and plasma sampling, no conclusion could be drawn regarding the distribution of the plasma-tissue relationship. Similar observations were made in a case of a kidney transplant recipient with invasive aspergillosis (Kuipers et al., 2011). Posaconazole concentrations in the liver were highest (18.4 μg/g tissue), followed by renal fat tissue (7.1 μg/g tissue), kidney (6.5 μg/g tissue), spleen (5.8 μg/g tissue) and lung (4.1 μg/g tissue) compared to whole blood (1.1 μg/mL). Interestingly, the lipophilic character of posaconazole and itraconazole could lead to a more pronounced accumulation of these drugs in adipose compartments, but studies with posaconazole have yielded contradictory data on a correlation between weight and posaconazole plasma concentrations (Payne et al., 2016; Sime et al., 2019; Tang et al., 2017; Wasmann et al., 2020). No data are available for itraconazole specifically in obese

patients. Nevertheless, since TDM is critical for the therapy with azole antifungals, as discussed in section 3.5, differences in plasma concentrations can be compensated between patients with different physiological conditions. Unfortunately, regarding the adverse mineralocorticoid excess effects, no data about the tissue accumulation in the adrenal glands are currently available.

Tissue concentrations can be influenced by a number of other aspects that should be kept in mind, such as pharmacological (*e.g.* route of administration) and physiological factors (*e.g.* age, underlying diseases), as well as interindividual variability in drug metabolism and interactions with drug transporters. Regarding the latter, itraconazole and posaconazole are substrates and inhibitors of the efflux pump P-glycoprotein (P-gp) (Lempers et al., 2016; Vermeer et al., 2016). P-gp is widely expressed in different tissues that have either an excretion or barrier function, including the adrenal glands, kidney and colon. This expression pattern suggests a protective role of P-gp for the host to avoid accumulation in mineralocorticoid tissues, and an impaired P-gp function or its inhibition by xenobiotics may promote the development of SME.

The role of genetic polymorphisms in the multidrug resistance (MDR) 1 gene (encoding P-gp) and the influence on the pharmacokinetics of posaconazole has been investigated in a few studies. Genetic polymorphisms of the MDR1 gene have been linked to significant variations in P-gp expression, with different allele frequencies between racial groups (Schaeffeler et al., 2001). However, Sansone-Parsons et al. observed no association between any MDR1 single-nucleotide polymorphism and plasma posaconazole concentration in healthy volunteers (Sansone-Parsons et al., 2007). Suh et al. also found that genetic polymorphisms of the MDR1 gene had no correlation with posaconazole plasma concentration in Korean patients (Suh et al., 2018). Besides MDR1, genetic variants have been described for almost all key uptake and efflux transporters, and some of these polymorphisms might affect the individual drug PK. Vermeer et al. evaluated the inhibitory capacities of itraconazole and its metabolites hydroxy-, keto-, and N-desalkyl itraconazole on 13 clinically relevant drug transporters (Vermeer et al., 2016). Interestingly, a comparison of the IC_{50} values of itraconazole and OHI showed a more pronounced inhibition of the transporters by OHI in all cases but for P-gp. Potentially clinically relevant interactions of itraconazole and OHI have been predicted with the following transporters: P-gp, organic cation transporter (OCT) 1, and breast cancer resistance protein (BCRP). A further potent (IC_{50} values in the lower nanomolar range) and potentially clinically relevant inhibition has been found solely for OHI with the organic anion transporting polypeptides (OATP) 1B1 and 1B3. Inhibition (with low micromolar IC_{50} values) of BCRP and the bile salt export pump (BSEP) by itraconazole, OHI and posaconazole has been confirmed by others (Lempers et al., 2016). However, the clinical relevance of these moderate inhibitory activities remain unclear. Regarding BSEP, studies investigating the mechanisms behind drug induced liver injuries found no inhibition of BSEP by itraconazole and posaconazole, but detected an inhibition of MDR3, with IC_{50} values in the lower micromolar range (Mahdi et al., 2016; Yoshikado et al., 2011). To date, studies assessing whether genetic polymorphisms play a role in the transporter-mediated uptake or reduced efflux of azole antifungals into the adrenals glands are lacking and such studies could provide information on the interindividual differences leading to SME.

Itraconazole is converted into its main active metabolite OHI by CYP3A4, which is then further sequentially metabolized by CYP3A4 to keto-itraconazole and N-desalkyl-itraconazole (Isoherranen et al., 2004). Itraconazole bears three chiral centers and is therefore applied as a racemic mixture of four diastereomers (two enantiomeric pairs) of which only two are metabolized by CYP3A4 (Kunze et al., 2006). All diastereomers showed antifungal activity *in vitro*, but the *cis* diastereomers, to which the latter two compounds belong, exhibit a higher antifungal potency than the *trans* diastereomers (Shi et al., 2010). Clinical studies for the registration of itraconazole revealed that the simultaneous administration of itraconazole together with strong inducers of CYP3A4 led to a reduced bioavailability of itraconazole and OHI by up to 90% (Janssen-Cilag-AG, 2019). This enzyme induction can last for up to 4 weeks after discontinuation of a CYP3A4 inducing drug, such as rifampicine, phenytoin, phenobarbital, carbamazepine or St. John's wort (*Hypericum perforatum*). Importantly, itraconazole, OHI and posaconazole are potent inhibitors of CYP3A4, leading to a number of clinically relevant drug–drug interactions. Although posaconazole inhibits CYP3A4 activity, its metabolism is primarily mediated through phase 2 biotransformations in the liver via UDP-glucuronyl-transferase (UGT) 1A4 (Ghosal et al., 2004). For the co-treatment with drugs that are also substrates of CYP3A4 or P-gp, a dose-reduction can be recommended. In this regard, the concomitant administration of posaconazole or itraconazole with the vinca alkaloid vincristine was found to cause excessive exposure to vincristine with severe neurotoxicity due to a reduced metabolism by CYP3A4 and impaired transport via P-gp (reviewed by (Moriyama et al., 2012)). Interestingly, hypertension occurred in 40% of these patients, but this has been attributed to the manifestation of the vincristine-associated autonomic neuropathy.

Current evidence suggests that variations in the CYP3A4 genotype contribute only by a minor extent or in rare cases to the interindividual differences in CYP3A4 activity, suggesting that itraconazole is only minimally affected by pharmacogenomics CYP3A4 polymorphisms (Amsden et al., 2017; Werk et al., 2014). However, a recent case report describes increased blood pressure and hypokalemia in a patient receiving itraconazole, who was later assigned with a CYP3A4 genotype*1/*22 that is associated with reduced CYP3A4 function (Teaford et al., 2020). The patient exhibited a total itraconazole/OHI serum level of 4800 ng/mL while on 400 mg itraconazole daily. A dose reduction to 300 mg/day even increased total itraconazole serum concentration to 7800 ng/mL. Further dose de-escalation steps to 200 mg daily revealed 6500 ng/mL total itraconazole levels and hypokalemia persisted also when the dose was further reduced to 100 mg daily. Even 17 days after stopping itraconazole therapy, the patient still had a total serum itraconazole level of 1400 ng/mL.

Regarding posaconazole, a polymorphism in the UGT1A4 gene has been described as a risk factor for being a poor absorber of this drug (Suh et al., 2018). The authors suggested that the genetic polymorphism of UGT1A4 could increase the clearance of posaconazole by promoting the glucuronidation efficiency. This polymorphism was further investigated by evaluating the impact of clinical variables on posaconazole plasma concentrations in Korean high-risk patients with hematologic malignancy (Chae et al., 2020). A higher prevalence of the UGT1A4*3 allele (33.0%) was found in patients with posaconazole plasma trough concentrations <500 ng/mL (defined as poor absorbers). Meletiadis et al. summarized the knowledge on pharmacogenomic variations and their influence on antifungal efficacy and proposed the following targets for the analysis of genetic polymorphisms as important for the pharmacokinetics of itraconazole and posaconazole: gastrointestinal pH, efflux transporter such as P-gp or BCRP, albumin, as well as enzymes involved in phase 1 and phase 2 metabolism (Meletiadis et al., 2006). However, intra- and interindividual differences leading in some patients to a posaconazole or intraconazole-dependent SME most likely involve various conditions and/or a combination of different factors. Clearly, further studies are required to elucidate the individual conditions that render some patients more susceptible to antifungal drug exposure.

3.5. Therapeutic drug monitoring

Due to these considerable interindividual differences, standardized antifungal dosage recommendations may not be able to ensure drug efficacy and safety in all patients. Furthermore, for some fungal infections an elevated minimum inhibitory concentration (MIC) may be necessary, thus requiring a higher drug exposure. The introduction of TDM may help improving the probability of an optimal clinical outcome. TDM can be considered for drugs with a confirmed exposure-response

relationship or a defined therapeutic range and is particularly indicated for drugs with a narrow therapeutic window, bioavailability concerns, substantial inter- or intra-patient pharmacokinetic variability, a potential for genetic polymorphisms to impact drug clearance, drug-drug interactions affecting antifungal serum concentrations, treatment failure, or symptoms of drug toxicity (John et al., 2019; Johnson et al., 2020). TDM may be performed as routine analysis or in specific subsets of patients such as patients with altered distribution volumes (*e.g.* critically ill patients with sepsis, obese patients) or with an impaired kidney or liver function. Trough levels may be measured after reaching steady-state conditions and repeatedly after 2–3 weeks of therapy to re-assess steady-state conditions. A continued monitoring or re-evaluation can be warranted upon therapy modifications (dosing, formulation or concomitant medication). Considering these points, there is clear evidence for clinical benefits of a TDM for the majority of patients treated with itraconazole or posaconazole. TDM of posaconazole is currently a subject of debate. Routine monitoring of plasma trough levels has been mainly recommended to ensure adequate drug exposure for patients receiving the oral posaconazole suspension solution, as administration of the newer delayed-release tablets or *iv* formulation leads to higher and more consistent plasma concentrations (Ullmann et al., 2018; Wiederhold, 2016). This has limited use of the oral suspension solution, *e.g.* for the treatment of pediatric patients. A recent study compared the variability of posaconazole delayed-release tablets and suspension formulation (Gautier-Veyret et al., 2019). Despite an increased posaconazole exposure with the tablet formulation, the variability of posaconazole trough concentrations was not significantly lower than that of the suspension formulation. Another study that analyzed TDM practice and exposure to posaconazole tablets also showed variable drug exposure (Martson et al., 2019). In addition, they described adequate therapeutic drug exposure (≥1500 ng/mL) in only 64% of the measured samples, and in 54% of these cases a dose change recommendation was suggested. However, when therapeutic concentrations of >1000 ng/mL were used, 90% of the samples were within the adequate range. Another study, determining the percentage of therapeutic posaconazole drug concentrations (>700 ng/mL) across all three drug formulations in a retrospective cohort study, described therapeutic levels for the oral suspension solution in 37% (14/38) of the cases, while 97% (28/29) of the *iv* solution and 82% (27/33) of the levels for the tablet formulation reached the therapeutic range (Yi et al., 2017). Although routine TDM could still be useful for all posaconazole drug formulations, it should be considered especially in cases of unresponsive treatment, pathogens with elevated MIC or occurrence of unexplained toxicity. Currently, no data are available defining an upper target level for posaconazole to avoid drug toxicity. As discussed in section 3.3 the provisional cutoff of 3750 ng/mL applied by PK studies to support the registration of the delayed-release tablets by the EMA (Cornely et al., 2016; Ullmann et al., 2018) is significantly higher than the serum posaconazole concentrations of ≥3000 ng/mL, which are reported to be associated with the occurrence of SME (Nguyen et al., 2020). Dekkers and colleagues have already suggested that the use of the new tablet and *iv* formulations may result in new adverse events (Dekkers et al., 2016), thus emphasizing the need for TDM.

Similarly, the limited data available for itraconazole supports a clear threshold for toxicity (John et al., 2019). Lestner et al. showed a progressive increase in the probability of the occurrence of toxicity with increasing concentrations of itraconazole in 216 patients examined (Lestner et al., 2009). Classification and regression tree analysis revealed an itraconazole concentration of 17.1 μg/mL, measured by bioassay, as an appropriate upper limit for TDM, since in their study 31% of the patients with concentrations <17.1 μg/mL developed toxicity, compared to 86% of the patients with concentrations ≥17.1 μg/mL. Bioassays measurements cannot distinguish between itraconazole, OHI and additional metabolites, resulting in values 2–10 times higher than those obtained by analytical methods, where both compounds are determined separately (Hostetler et al., 1993; Law et al., 1994; Odds et al., 1999; Wiederhold et al., 2014). While the Infectious Diseases Society of America recommends the sum of both itraconazole and OHI concentrations for the assessment of the drug level, most other guidelines refer only to itraconazole concentrations, which might lead to an underestimation (Ashbee et al., 2014; Pappas et al., 2016; Ullmann et al., 2018; Wheat et al., 2007). As only few cases of itraconazole-dependent SME have been reported so far, more data are needed to demonstrate a dose-dependent incidence of the phenotype. In addition, further studies are required to 1) determine upper target concentrations for TDM of both posaconazole and itraconazole, without compromising the clinical efficacy for the treatment of pathogens with variable MIC, and 2) develop a clear TDM strategy for the different drug formulations and therapeutic purposes.

4. Topically applied azole antifungals

The majority of antifungal drugs available on the market are approved for topical or vaginal use. Their systemic absorption is generally much lower than 10% of the administered dose, with the exception of miconazole when applied as oral gel, where the absolute bioavailability is approximately 25–30% (Bayer-AG, 2014; Croxtall et al., 2009; Janssen-Cilag-AG, 2016; Janssen-Cilag-AG, 2017; Janssen-Cilag-AG, 2018; Patzschke et al., 1983; Stevens et al., 2002). Therefore, the risk of developing SME during the therapy with azole antifungal drugs for mucosal and cutaneous infections can be considered very low, and no clinical cases with mineralocorticoid excess symptoms or other obvious endocrine disturbances have been reported so far.

Nevertheless, several *in vitro* studies showed potent interferences of certain topical azole antifungals with adrenal and gonadal steroid biosynthesis, although there were some discrepancies between the studies, likely due to differences in assay performance and species effects. Clotrimazole and miconazole were found to inhibit the activities of CYP11B1, CYP17A1 and CYP19A1 (Denner et al., 1995; Erdmann et al., 1995; Mason et al., 1985, 1987; Morishita et al., 2001; Trosken et al., 2004; Vanden Bossche et al., 1989; Wada et al., 1988). Moreover, one study suggested that miconazole can inhibit 21-hydroxylase activity, based on experiments in human adrenal cells from a patient with CS (Lamberts et al., 1987). Further capacities to inhibit CYP17A1 and CYP19A1 were detected for bifoconazole and econazole. Unfortunately, other topically applied azole antifungals have been less investigated for their potential to interfere with steroidogenesis. Tioconazole and isoconazole have been reported to inhibit CYP17A1 activity, whereas a very weak inhibition of 11β-HSD type 1 or type 2 has been found for climbazole (a substrate of 11β-HSD1 (Meyer et al., 2013)), tioconazole, sertaconazole and butoconazole (Ayub et al., 1987; Beck et al., 2017).

Systemic concentrations of these topical azole antifungals may be too low to cause adverse effects by disturbing adrenal steroidogenesis; however, drugs may reach substantial levels in skin because of the route of exposure and due to accumulation. Steroidogenesis in the skin is almost identical to that in the adrenal cortex, and human skin expresses all key steroidogenic enzymes, *i.e.* CYP11A11, 3β-HSD1, CPY17A1, CYP21A2 and CYP11B1 (reviewed by (Nikolakis et al., 2016; Slominski et al., 2013; Slominski et al., 2014)). Skin cells also express 11β-HSD type 1 and 2, permitting rapid activation or inactivation of glucocorticoids, depending on skin cell type (reviewed by (Slominski et al., 2014; Terao et al., 2016; Tiganescu et al., 2011)). Steroid production in skin seems to be highly context and cell type dependent. Interestingly, a gradual increase in CYP11B1 expression has been shown in the case of an acute skin injury and acceleration of wound healing was observed by topical application of CYP11B1 inhibitors (Emmerich et al., 2018; Vukelic et al., 2011). This is in line with the known adverse effects of pharmacological doses of glucocorticoids on wound healing (Hengge et al., 2006). Other studies reported elevated 11β-HSD1 expression in aging skin and during wound healing, and inhibition of this glucocorticoid activating enzyme resulted in the improvement of several skin health parameters as well as in enhanced wound healing in mice

(Boudon et al., 2017; Terao et al., 2011; Tiganescu et al., 2013, 2014). The relative contribution of CYP11B1- and 11β-HSD1-dependent glucocorticoid production in the wound healing process and in aging remains unclear; however, inhibition of these enzymes may be beneficial in this respect. Thus, inhibitors of CYP11B1 and 11β-HSD1 such as miconazole and climbazole may not only be effective in treating cutaneous fungal infections, but may also promote wound healing. Clearly, further studies are required to investigate this hypothesis.

Ketoconazole has a distinct position among the topically applied azole antifungals, as it was initially introduced for systemic applications (Heeres et al., 1979; Symoens et al., 1980). Shortly after market launch, low testosterone concentrations, occurrence of gynecomastia, and glucocorticoid suppression were reported in several studies on long-term ketoconazole treatment (DeFelice et al., 1981; Pont et al., 1982; Pont et al., 1982, 1982; Santen et al., 1983). The potent inhibition of adrenal and gonadal activities of CYP11A1, CYP17A1 and CYP11B1 were found to cause these adverse effects (Engelhardt et al., 1991; Feldman, 1986; Loose et al., 1983). Due to the inhibition of these enzymes, ketoconazole was then used on an off-label basis for the treatment of CS (reviewed by (Daniel et al., 2015, 2014)). Two early studies described sustained hypertension in a small subset of patients who had elevated concentrations of 11-deoxycortisol and DOC but significantly decreased cortisol along with normal aldosterone levels during long-term or high-dose treatment with ketoconazole (Aabo et al., 1987; Leal-Cerro et al., 1989). However, a recent retrospective multicenter study involving 200 patients reported that 50% and 61.6% of the patients receiving ketoconazole as pre-surgical treatment (n = 40) had unresolved hypertension and hypokalemia, whereas about 60% of patients receiving ketoconazole as primary or secondary treatment (n = 160) exhibited hypertension and hypokalemia (Castinetti et al., 2014). Due to concerns of severe hepatotoxicity, the EMA and the FDA restricted the systemic application of ketoconazole for the therapy of fungal infections; however, the EMA approved oral ketoconazole for the therapy of CS due to the limited alternative options. Recent advances in CS therapy such as the approval of osilodrostat now provide alternative treatment options (Pivonello et al., 2020).

5. Conclusions

Inhibition of CYP11B1 and 11β-HSD2 by posaconazole and itraconazole has been found to cause a phenotype of mineralocorticoid excess. The dose-dependent incidence of SME during posaconazole and itraconazole therapy allows for a dose de-escalation strategy with simultaneous TDM to resolve the mineralocorticoid excess symptoms and to ensure efficient antifungal treatment. Since the incidence of SME during azole antifungal therapy is not a class-dependent effect, substitution of posaconazole and itraconazole therapy with fluconazole, isavuconazole or voriconazole could lead to a resolution of the SME phenotype. In SME affected patients, first-line antihypertensive treatment may include the administration of the mineralocorticoid receptor antagonist spironolactone and potassium supplementation (except for patients receiving abiraterone where spironolactone may promote prostate cancer growth) (Beck et al., 2020). However, eplerenone, another more selective mineralocorticoid receptor antagonist, is metabolized by CYP3A4 and should not be used to control hypertension caused by SME in combination with CYP3A4 inhibitors such as the azole fungicides. To address volume retention and edema, potassium-sparing diuretics might be applied, particularly in situations of hypokalemia. Moreover, additional studies are crucial to further investigate the inter- and intra-individual differences leading to SME under therapy with posaconazole and itraconazole and to determine upper target concentrations for TDM in order to be able to develop a clear TDM strategy for the different drug formulations and therapeutic purposes of posaconazole and itraconazole.

Author contribution statement

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Declaration of competing interest

None.

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