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PHARMACOLOGY AND PHARMACODYNAMICS OF ANTIFUNGAL AGENTS (P GUBBINS, SECTION EDITOR)

Cardiotoxicity Induced by Antifungal Drugs

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Abstract This review addresses the potential of antifungal drugs to cause cardiac toxicity. Many antifungal drugs, especially antifungal azoles, rarely cause torsades de pointes (TdP) and carry the risk of sudden death. Interventions to avoid TdP should include cautious use of azoles in combination with other drugs that cause QTc prolongation, and elimination of risk factors for TdP whenever possible. These risk factors include: hypokalemia, hypomagnesemia, severe bradycardia, and preexisting long QT syndrome. ECG monitoring should be considered when the use of multiple QT-prolonging drugs is unavoidable and TdP risk factors cannot be resolved. Itraconazole exhibits negative inotropic activity which may present as worsening heart failure in patients with preexisting heart failure. A few cases of severe bradycardia have also been described with voriconazole. Most cases of cardiac toxicity associated with amphotericin B are due to severe electrolyte abnormalities, rapid administration or overdose. Although cardiac toxicity is not common with the use of antifungal drugs, recognition of the potential to cause serious cardiac-related outcomes, evaluation of risk factors, and monitoring is warranted.

Keywords Antifungal drugs · QT · Heart failure · Cardiac toxicity · Fluconazole · Ketoconazole · Itraconazole · Voriconazole · Posaconazole · Amphotericin B · Ehinocandins

Introduction

Antifungal drugs have been implicated in causing cardiotoxicity. Azole antifungal drugs can directly prolong the QT interval and cause drug–drug interactions leading to increased exposure to other drugs that also prolong the QT interval. Amphotericin B may lead to arrhythmias through indirect mechanisms including cytokine release and electrolyte abnormalities. Fungal infections tend to occur in patients with multiple medical problems and with polypharmacy ensuring the presence of several risk factors for drug-induced cardiotoxicity. This review focuses on the pathophysiology and clinical manifestations of drug-induced cardiotoxicity related to the use of antifungal agents.

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Cardiac Electrophysiology

Electrical impulses are generated by specialized conduction tissue in the heart and the impulse is rapidly spread throughout the heart chambers. The impulse, normally initiated at the SA node, distributes rapidly through the two atria and to the AV node. This current causes the left and right atria to contract, filling the right and left ventricles with blood. The impulse is momentarily delayed at the AV node before being transmitted over both ventricles through the left and right bundle branches and Purkinje fibers leading to contraction of both ventricles. Electromechanical coupling ensures that depolarization of the muscle cells produces contraction followed by repolarization so that the muscle cells are ready for the next impulse. Heart rhythm is usually measured with surface electrodes (electrocardiogram, ECG). A normal ECG tracing includes a p wave (SA node, atrial depolarization), QRS complex (ventricular depolarization) and T wave (heterogeneous repolarization). The QT interval encompasses ventricular depolarization and repolarization, whereas the QRS duration reflects depolarization, which is normally rapid (<12 ms). Most of the QT interval reflects repolarization and defects in this process result in vulnerability to serious cardiac arrhythmias. Problems may occur if the QT interval is too short or too long. The most common drug-induced abnormality involves prolonged QT often with ST segment changes and perhaps the addition of a U wave, which should be included when measuring the QT interval (i.e. QT(U)interval) [1].

At the heart of QT prolongation is a defect in repolarization [2]. Depolarization results from rapid cellular influx of sodium

and calcium, countered by the out flux of potassium. Several membrane channels including the I_{Kr} and I_{Ks} are responsible for ion movement . Although congenital long QT syndrome may result from gene mutations controlling these and other channels, I_{Kr} is involved in nearly all drug-induced cases of long QT syndrome. Drugs can block the I_{Kr} channel or interfere with its function indirectly. The physiology and structure of the I_{Kr} channel is extensively reviewed elsewhere [3•]. Preclinical screening of drugs for their potential to affect the I_{Kr} current can be done using a patch clamp assay. This involves an isolated cardiac muscle cell bathed in an electrolyte solution with a microelectrode inserted inside the cell and a reference electrode in the surrounding bath. Current pulses are introduced and changes in the intracellular potential differences are measured in the presence of increasing drug concentrations, which ultimately produces an IC_{50} value. Unfortunately, many drugs have an effect on I_{Kr} function at relevant concentrations, and simply abandoning a drug that blocks I_{Kr} is not a wise decision.

The QT interval exhibits some variation with time of day, heart rate and unexplained factors. In particular, the QT interval varies inversely with heart rate. A number of correction factors have been used to facilitate interpretation. The most widely used correction methods are the QTc-B (Bazett) and QTc-F (Fridericia) where $QTc=QT/RR^{1/2}$ and $QT/RR^{1/3}$, respectively. A normal QTc interval ranges from 430 to 450 ms. In prepubertal children there is no difference by sex and the typical value is 440 ms. A typical value for adult men is 430 ms, while adult women have a larger typical value of 450 ms [1]. Most clinicians would consider a QT interval of >500 ms as prolonged; however, prolonged may be defined as an increase of as little as 20 ms over the typical values listed above [4, 5]. A prolonged QTc interval may be described as an acquired or congenital long QT syndrome. Patients with drug-induced prolonged QTc interval represent a large proportion of those with an acquired form [6]. There are a number of genetic mutations responsible for congenital long QT syndrome [5, 7–9]. Preexisting long QT syndrome is a known risk factor for serious cardiac arrhythmias and clinicians need to exercise extreme care when using drugs that further prolong QT intervals in this population. Estimates of the number of patients with genetic mutations associated with long QT interval that has a silent presentation with a normal QTc interval have ranged from 10 % to 50 % [7]. These individuals may have enhanced sensitivity to drug-induced QT prolongation.

Individuals with either acquired or congenital long QT syndrome are at increased risk of torsades de pointes (TdP), which is a distinctive polymorphic ventricular tachycardia. TdP may result in dizziness, lightheadedness or syncope and may be transient. Alternatively, TdP may degenerate into ventricular fibrillation and can cause sudden death. The ECG records the net electrical activity generated by the heart and transmitted through the thorax and chest wall. The heart chambers are surrounded by epicardial, transitional, M, and endocardial cell layers, and these have distinctive action potentials. The M cells tend to have more prolonged repolarization particularly in response to slowed heart rate or exposure to agents that cause prolonged QT [10].

The most common form of drug-induced long QT syndrome can be studied in animal models using D-sotalol to block I_{Kr}. This drug causes prolonged action potential in all cell types, but more pronounced in the M cell. D-Sotalol produces slowing of the phase 3 of the action potential resulting in low amplitude T-waves, long QTc interval, and the addition of a U-wave. The QT(U)c interval appears to be important since the U-wave represents further repolarization heterogeneity. Generation of TdP is often associated with early after depolarization and high variability in cycle to cycle QT(U) intervals. Factors that predispose to TdP generation include bradycardia, variable cycle intervals (especially short–long-short), drug-induced long QTc interval, hypokalemia, and hypomagnesemia. TdP can be reproduced experimentally in a canine model. The AV conduction pathway is damaged leading to chronic AV block and bradycardia. Subsequently, D-sotalol is administered to prolong QTc and ventricular pacing is used to mimic the short–long–short–cycle. Administration of D-sotalol without pacing causes a small frequency of TdP (about 5 %); however, with pacing a high incidence of TdP can be reproduced. Both increased heart rate (isoproterenol) and magnesium can suppress the induction of TdP in this model [11]. The short-term variability in action potential duration in M cells may be the best predictor of potential for drug proarrhythmic effects [12]. I_{Ks} plays little role in normal repolarization, while I_{Kr} plays the central role. When the QT interval is prolonged, however, I_{Ks} becomes an important back-up system to ensure final repolarization [13]. This raises the concern that existing (sometimes silent) mutations of genes that encode I_{Ks} may underlie many cases of drug-induced TdP. Class 3 antiarrhythmic drugs such as dofetilide and ibutilide can induce TdP in about two-thirds of dogs without pacing.

QT-prolonging effects of a drug are considered a “mediocre” predictor of TdP risk [14]. Amiodarone, for example, may cause pronounced QT prolongation, but because it reduces heterogeneity of repolarization, amiodarone infrequently results in TdP. At the other extreme, a drug (e.g. azithromycin) can have a minimal QTc-prolongation effect and result in TdP and a fatal outcome. Nonetheless the extent of QT prolongation generally correlates with the risk of TdP. For drugs with high potential to cause QT prolongation, the likelihood of TdP being detected in the clinical setting is quite low [1, 14, 15]. The typical non-antiarrhythmic drug causes TdP in less than 1 in 10,000 to 1 in 100,000 exposures. Thus, detection of this clinical adverse event in clinical trials in which the number exposed is in the 2,000 – 3,000 range is unlikely [14]. Diagnosis of TdP requires capture of the event with ECG recording. Some TdP events are silent and transient, or may be self-limited, causing dizziness,

lightheadedness or syncope. In the absence of ECG recording, these events may be attributed to other problems. In addition there may be cases of sudden death caused by TdP/ventricular fibrillation where the contribution of a drug-related adverse event is never considered. In Europe and North America, sudden cardiac death occurs in about 1 in 1,000 of the population over the age of 35 years. At least half of these events are related to ventricular tachycardia or ventricular fibrillation [16]. The extent that drug-induced arrhythmias and TdP contribute to this mortality is unknown. Most reports of TdP are spontaneous reports in which the number of cases relative to the number of exposures is never really known, and thus the true incidence of TdP is not known.

A different approach to the risk of cardiotoxicity involves analysis of large datasets from insurance claims. Concomitant use of a CYP34A inhibitor and erythromycin leads to a fivefold greater risk of sudden death compared to amoxicillin use; however, there were only three deaths among 194 subjects exposed to the potential interaction [17]. A similar study involving azithromycin was performed and demonstrated that the excess risk of death due to ≤5 days of azithromycin exposure is about 1 in 21,000. This study was done in a relatively healthy population of patients treated for respiratory tract infections. Similar population-based estimates are not available for most drugs with potential to increase QTc interval [18]. No studies of this type have been performed with antifungal drugs.

Antifungal Drugs

Azoles

Fluconazole, the most widely used systemic antifungal drug, directly inhibits I_{Kr} current (IC_{50}=48.2 μM=14.8 μg/ml) and alters protein trafficking [19]. Although, fluconazole is considered a low potency inhibitor based on the IC_{50} value, the inhibition occurs at concentrations readily achieved in clinical practice [20]. Fluconazole development occurred prior to the requirement for a thorough QT study and what is known comes mostly from case reports. During a 4-year period, 48 cases of TdP were reported to the US FDA [21]. One study examined QTc intervals on day 7 of treatment for cryptococcal meningitis in AIDS patients. There was no significant change in QTc for amphotericin B or the combination of amphotericin B and 400 mg/day of fluconazole. The change in QTc with amphotericin B + fluconazole 800 mg/day averaged +13.4 ms (QTc_B, 95 % CI 0.5 to 26.3 ms) [22]. Table 1 provides a summary of the reported cases of TdP suspected to be caused by fluconazole. Most of the patients were women and women have a higher risk of TdP in general [42]. There were occasionally concomitant drugs that may have contributed to prolonged QT; however, there was at least a temporal association with fluconazole administration. In one patient, TdP occurred with concomitant administration with domperidone, a gastrointestinal prokinetic agent known to be associated with QT prolongation; however, TdP recurred later with administration of fluconazole alone [32]. Fluconazole is a weak inhibitor of CYP3A4 and a strong inhibitor of CYP2C9. Considering the reported concomitant drugs, it is unlikely that pharmacokinetic drug–drug interactions were responsible for TdP development.

Ketoconazole inhibits I_{Kr} current directly and through inhibition of protein trafficking. The IC_{50} has been reported to be 1.92 μM (1.02 μg/ml), which makes ketoconazole a more potent I_{Kr} current inhibitor than fluconazole [43]. The *C*max after administration of 200 and 400 mg tablets averages 3.8 and 9.9 μg/ml, respectively, which would be expected to increase slightly with multiple daily dosing [44]. In a conscious guinea pig model, ketoconazole 200 mg/kg did not affect the QT interval [45]. However, the lack of toxicokinetic measurements diminishes the ability to interpret these findings based on whether serum concentrations were in the range of those seen with clinical use. In a group of 26 and 30 healthy subjects, administration of ketoconazole resulted in a mean increase in individualized QTc of 6.96 and 7.52 ms, respectively (95 % CI 3.31 – 10.62 ms and 4.15 – 10.89 ms) [46]. A thorough QT study was performed to evaluate the effects of bilastine, a H1 receptor antagonist approved in Europe, on QTc, and this study included concomitant administration with ketoconazole as a CYP3A4 inhibitor. The maximum change in individual normalized QTc was 3.5 ms (95 % CI 0.6 to 6.3 ms) with bilastine 20 mg, 5.0 ms (2.2 to 7.9 ms) with bilastine 100 mg, 9.3 ms (6.5 to 12.2 ms) with the combination of bilastine 20 mg and ketoconazole 400 mg, and 20.7 ms (17.9 to 23.6 ms) with moxifloxacin 400 mg. Since a significant change was defined as an upper 90 % CI change of more than 10 %, the change with the combination involving ketoconazole was considered significant. Although ketoconazole administration resulted in a 2.5-fold increase in bilastine *C*max, the *C*max of bilastine was still less than 40 % of that resulting from administration of the 100-mg dose of bilastine which did not have a significant effect on QTc. Either ketoconazole was responsible for prolonging QT or the combination of normal dose bilastine and ketoconazole was required [47]. With any interpretation the effect of ketoconazole was considerably less than that of moxifloxacin.

One case of ketoconazole-induced TdP did not involve a drug–drug interaction as the primary cause. The case patient was taking concurrent cetirizine which has not been linked with QT prolongation [35]. Ketoconazole is a very potent inhibitor or CYP3A4 and many cases of QT prolongation have been reported in patients receiving a drug with QT prolongation potential and increased drug exposure resulting from an interaction with ketoconazole. In a 2006 review,

Table 1 Reported cases of TdP related to the use of antifungal azoles

Patient		Drugs associated with QT prolongation	Other risk factors	Reference
Sex	Age (years)			
Female	68	Fluconazole (600 mg)	None	[23]
Female	25	Fluconazole, amiodarone	History of ventricular tachycardia/fibrillation, hypokalemia, hypomagnesemia, bradycardia	[24]
Female	57	Fluconazole, amitriptyline	Bradycardia, hypokalemia	[25]
Male	11	Fluconazole, amiodarone	Hypokalemia	[26]
Male	53	Fluconazole, levofloxacin	End-stage renal disease/hemodialysis	[27]
Female	59	Fluconazole (serum concentration 216 μg/ml)	Liver cirrhosis	[28]
Female	68	Fluconazole	None	[29]
Female	69	Fluconazole, sevoflurane	?Silent long QT syndrome	[30]
Female	26	Fluconazole	Hypokalemia	[31]
Female	33	Fluconazole, domperidone	None	[32]
Female	55	Fluconazole (200 mg×1)	Hypokalemia	[33]
Female	25	Fluconazole (400 mg/day)	Dilated cardiomyopathy, congenital long QT syndrome, prior TdP (hypomagnesemia, erythromycin)	[34]
Female	63	Ketoconazole (200 mg twice daily)	Coronary artery disease	[35]
Female	15	Voriconazole (6 mg/kg twice daily)	Bradycardia (28 bpm), hypokalemia, ciprofloxacin, ?ondansetron	[36]
Male	15	Voriconazole (6 mg/kg×1)	None	[37]
Female	12	Voriconazole	Hypokalemia, hypomagnesemia, ciprofloxacin, prolonged QT, trigeminy	[37]
Female	62	Voriconazole (200 mg twice daily)	Acute cardiomyopathy (ejection fraction 25 – 30 %), hypokalemia, borderline hypomagnesemia	[38]
Female	34	Voriconazole	Hypomagnesemia	[39]
Male	57	Voriconazole, methadone	Bradycardia	[40]
Female	14	Voriconazole (serum concentration 7 μg/ml), posaconazole (200 mg×1)	Hypomagnesemia, concomitant posaconazole during treatment transition	[41]

13 cases of ketoconazole-related TdP were reported to have involved concurrent administration of nonsedating antihistamines, terfenadine and astemazole [48]. Both of these antihistamines were removed from the US market due to risk of QT prolongation and TdP, primarily when administered with CYP3A4 inhibitors such as ketoconazole and itraconazole. There was also one case related to drug interaction with cisapride [48]. Cisapride was initially removed from the US market in 2000, but is currently available through a limited access protocol. In 2013, the US FDA moved to restrict ketoconazole use based on risk of hepatotoxicity, adrenal insufficiency and drug–drug interactions (http://www.fda.gov/Drugs/DrugSafety/ucm362415.htm, accessed 26 March 2014). Coadministration of dofetilide, quinidine, pimozide, and cisapride are listed as contraindicated. Terfenadine was previously removed from the market due to QT prolongation and TdP risk, and concomitant ketoconazole contributed to TdP development in many of the reported cases, and QT prolongation in interventional studies. Clinicians need to be careful with any drug that carries the potential to prolong QT interval and is metabolized to a large extent by CYP3A4 enzymes. The FDA has also recommended against using ketoconazole as a positive control in drug interaction studies due to risk of serious toxicity (http://www.fda.gov/drugs/drugsafety/ucm371017.htm, accessed 26 March 2014).

No cases of direct itraconazole-induced QT prolongation were found in the literature. Itraconazole, like ketoconazole, is a strong inhibitor of CYP3A4 that may contribute to QT prolongation by causing a pharmacokinetic drug–drug interaction. A 2006 review cited three cases of TdP involving itraconazole and terfenadine [48]. Itraconazole has also been reported to induce QT prolongation and TdP when given in combination with methadone [49], quinidine [50, 51], amiodarone [52], terfenadine [53], and haloperidol [54]. In the case of haloperidol, which is metabolized by CYP2D6 and CYP3A4, the presence of slow metabolizer phenotype (CYP2D6*10/*10) and itraconazole together produced more than a threefold greater exposure (AUC) to haloperidol, but did not result in greater maximum QTc change. This study involved a single dose of haloperidol and there were minimal changes in *C*max in the different treatment groups [54]. The risk of QT prolongation could be substantial with concomitant administration and accumulation of haloperidol if no interventions were taken to avoid this potential interaction.

Itraconazole has been associated with new and worsening cases of heart failure [4, 55]. By 2001, 58 cases of possible

itraconazole-induced heart failure had been reported to the FDA. Itraconazole has a direct negative inotropic effect in the isolated rabbit heart and in conscious dogs [56]. The usual presentation of worsening heart failure occurs in a person with a history of congestive heart failure, diabetes, and/or hypertension [57]. One case involved a 22-year-old man with HIV infection, who had been found to be HIV-positive 14 months earlier and was considered asymptomatic. He presented with pulmonary congestion and acute heart failure and was diagnosed with histoplasmosis. His ejection fraction was 45 % by transthoracic echocardiography and he rapidly responded to diuretics and fluid management. Upon transfer from the ICU to a ward, the patient's antifungal therapy was changed from amphotericin B to itraconazole. Within 5 days, he developed signs and symptoms of acute congestive heart failure with an ejection fraction of 30 %. The patient died of asystolic cardiac arrest [58]. Another case of heart failure was precipitated over 5 days in a 60-year-old woman treated for onychomycosis with 400 mg/day of itraconazole [55].

Voriconazole was not found to inhibit I_{Kr} current in a patch-clamp assay. In the same study, ketoconazole served as a positive control and did inhibit I_{Kr} current (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-266_VFEND_medr_P2.pdf, p. 9–10; accessed 26 March 2014).

Cases of voriconazole-induced TdP have been reported (Table 1). One case of TdP and cardiac arrest was reported in a 14-year-old girl within 30 minutes of a first dose of posaconazole; however, this occurred after a change from voriconazole, and the voriconazole serum concentration (7 μg/ml) was still elevated at 15 hours after administration [41]. TdP in this young girl was most likely due to voriconazole. There are two reports of severe bradycardia, one without significant QTc prolongation or TdP [59] and one with prolonged QTc and TdP [36]. There was no other apparent reason to explain the bradycardia with a heart rate of 28 bpm [36]. Voriconazole is metabolized by CYP2C19 which has polymorphic expression. Individuals with slow metabolizer phenotype may achieve considerably higher voriconazole concentrations than individuals without this variant. At this point there is no convincing evidence that the risk of cardiotoxicity with voriconazole is concentration-dependent. Voriconazole is a moderate inhibitor of CYP3A4 and strong inhibitor of CYP2C9, 2C19, and 2B6 [60]. Consequently, voriconazole coadministration may increase the exposure to other QT-prolonging drugs through a pharmacokinetic drug–drug interaction.

Posaconazole has been associated with a low potential (≤1 %) of QTc prolongation in phase I and clinical studies [61, 62]. On preclinical testing, no evidence was found for QT prolongation. The FDA-approved labeling provides a class statement (precaution) that some azole antifungal drugs including posaconazole have been associated with QT prolongation. There is one case of TdP reported in a patient with complications making the relationship to posaconazole difficult to ascertain (Noxafil® prescribing information; Schering Corp, 2008).

Although not intended as a comprehensive list, agents that have at least moderate potential to inhibit I_{Kr} and cause TdP, and that are subject to azole drug interactions are listed in Table 2. Antifungal azoles have the potential to inhibit metabolism by CYP3A4 (ketoconazole, itraconazole, others to a lesser extent), and CYP2C9 and CYP2C19 (voriconazole and fluconazole). The azoles may interact with these drugs by additive pharmacodynamics or pharmacokinetic interactions. Table 2 summarizes the documented and expected effects of antifungal azoles on these drugs. Risk of fungal infection is somewhat associated with risk of bacterial infection; thus patients who are receiving antifungal azoles for treatment or prophylaxis may also receive a fluoroquinolone. The potency of antifungal azoles to prolong QT interval decreases in the following order: moxifloxacin > gemifloxacin > levofloxacin > ciprofloxacin [63, 64]. Concurrent administration of a fluoroquinolone (levofloxacin most often) and an azole (fluconazole or voriconazole) was associated with a clinically important increase in QTc in one institution. Levofloxacin combined with fluconazole was associated with a mean increase in QTc of 9.5 ms (2.2 – 16.9 ms) with ten events considered clinically significant based on a change in QTc of 30 – 59 ms. Although the mean change in QTc was not significant for voriconazole there were still ten patients with a change in QTc of 30 – 60 ms and one with a change of >60 ms [85].

The macrolides, including erythromycin, clarithromycin, and azithromycin, are also widely used in patients who may receive antifungal drugs. However, population-based studies have shown the use of macrolides to be associated with excess cardiovascular deaths [14, 17, 18]. Specifically, the risk of cardiovascular death in patients receiving erythromycin was twice that of patients not receiving erythromycin during the observation period. Furthermore, the risk of cardiovascular death was elevated more than fivefold in patients receiving a CYP3A4 inhibitor along with erythromycin. The list of CYP3A4 included antifungal azoles, but the number of patients by inhibitor was not provided [17]. A similar study was completed for azithromycin; however, azithromycin is not metabolized by CYP3A4. Azithromycin use was associated with excess cardiovascular death of 47 per million treatment courses. A trend towards increased cardiovascular death has been noted with levofloxacin but not with ciprofloxacin [18].

Amphotericin B Formulations

Amphotericin B deoxycholate or lipid formulations of amphotericin B have been associated with cardiac arrhythmias. Generally these have occurred in the setting of rapid infusion or overdose. In one study, 27 patients received amphotericin B

Table 2 Agents most associated with TdP and concerns with respect to drug interactions with azole antifungal drugs [63–65] (http://www.crediblemeds.org/healthcare-providers, accessed 26 March 2014)

Drug class	Drug	Metabolic pathway	Pharmacokinetic drug interactions
Antiarrhythmic (class I)	Quinidine	CYP3A4	Itraconazole: *C*max ↑32 %; AUC ↑158 % [66]. Itraconazole: *C*max ↑59 %; AUC ↑142 % [51]
	Procainamide/*N*-acetylprocainamide	CYP2D6 + renal	Inhibition not expected (CYP 2D6) [67], 50 % renal.
	Disopyramide	CYP3A4 + renal	Unknown interaction, metabolism inhibited in vitro by ketoconazole [68]
Antiarrhythmic (class III)	Sotalol	None (mostly renal)	Inhibition not expected [69]
	Dofetalide	Renal + Minor CYP3A4	Ketoconazole: *C*max ↑53 – 97 %; AUC ↑41 – 69 %; also decreased renal clearance (Tikosyn prescribing information; Pfizer, NY, NY; 2013)
	Ibutilide	Non-CYP450, undefined	Inhibition not expected [70]
Antipsychotic	Haloperidol	CYP3A4, 2D6	Itraconazole: ↑*C*max 23 %; ↑AUC 23 %; more pronounced in CYP2D6 poor metabolizer [54]
	Thioridazine	CYP1A2, 2C19, 2D6	Fluconazole/voriconazole theoretical – inhibition of 2C19 seen with fluvoxamine [71]
	Ziprasidone	CYP3A4	Ketoconazole: ↑*C*max 34 %; ↑AUC 33 % [72]
	Quetiapine	CYP3A4, 2D6	Ketoconazole: *C*max ↑235 %; AUC ↑549 % [73]
	Respiridone	CYP3A4	Ketoconazole: *C*max ↑32 %; AUC ↑67 % [74]. Itraconazole: concentration ↑69 – 75 %, enhanced in CYP2D6 poor metabolizer [75]
Narcotic analgesic	Methadone	CYP2B6	Voriconazole: *C*max ↑31 %; AUC ↑47 % [76]. Fluconazole: ↑27 %; AUC ↑35 % [77]
Macrolide antibiotic	Erythromycin	CYP3A4	Voriconazole: ↑exposure to voriconazole, enhanced in CYP2C19 poor metabolizer [78]. Expected interaction with itraconazole and ketoconazole [17]
	Clarithromycin	CYP3A4	Theoretically similar to erythromycin
Pentamidine (intravenous)		CYP2C19	Theoretical for fluconazole and voriconazole by inhibition of 2C19 [79]
Fluoroquinone	Moxifloxacin	Non-CYP450	No interaction suspected [80]
	Gemifloxacin	Non-CYP450	No interaction suspected
	Levofloxacin	Non-CYP450	No interaction suspected
Antimycobacterial agents	Chloroquine	CYP2C8, 3A4, 2D6	Inhibition by itraconazole, ketoconazole likely [81, 82]
	Mefloquine	CYP3A4	Ketoconazole: ↑*C*max 79 %; ↑AUC 64 % [83, 84]

deoxycholate, 0.27 to 0.89 mg/kg over 1 hour, and ECG monitoring was done during the infusion. No arrhythmias were detected [86]. A single case of TdP associated with use of amphotericin B and flucytosine has been reported [48]. Cardiac arrest has been reported in a 4-year-old boy after administration of liposomal amphotericin B over 1 hour. His serum potassium was 16 mEq/L during resuscitation. The same authors reported a case involving amphotericin B deoxycholate, 1 mg/kg, in a 2-year-old girl which led to a serum potassium of 6.7 mEq/L after a 2-h infusion. The girl had end-stage renal disease and was undergoing hemodialysis. Administration of the amphotericin B during hemodialysis was done to successfully manage the hyperkalemia [87]. Repeated episodes of hyperkalemia associated with the infusion of liposomal amphotericin B have been reported in a 36-year-old man. Eventually, this led to an episode of refractory hyperkalemia and fatal cardiac arrest [88]. A 72-year-old woman developed chest pain, dyspnea, and feeling of impending death after administrations of both amphotericin B colloidal dispersion and liposomal amphotericin B; however, the patient was able to tolerate conventional amphotericin B [89]. Amphotericin B deoxycholate was associated with frequent premature ventricular contractions in an infant receiving normal doses [90]. Also an elderly woman developed two episodes of transient asystole associated with amphotericin B infusion. Her serum potassium and digoxin concentrations were elevated [91]. Two cases of dilated cardiomyopathy and heart failure related to liposomal amphotericin B treatment have been reported. These occurred in a 64-year-old man and a 23-year-old woman and resolved after treatment [92]. Whether amphotericin B affects the QT interval has not been reported in the literature.

After lipid formulations of amphotericin B became available, several medication errors occurred where conventional

amphotericin B was administered in place of a lipid formulation. The dose from lipid formulations is typically five times higher than from conventional amphotericin B, and this has led to a number of overdoses. Cardiac arrhythmias, and death were commonly seen in these situations [93–95]. In one case series, five infants/children received doses of amphotericin B deoxycholate ranging from 4.6 to 40.8 mg/kg and four of the five died. A 60-year-old woman received 4.3 mg/kg of conventional amphotericin B as a medication error leading to hemolysis, cardiovascular collapse, cardiac arrhythmias, and severe electrolyte abnormalities. Several courses of plasmapheresis and hemodialysis were utilized and the patient survived [96].

Flucytosine

No published reports of the effect of 5-flucytosine on the QT interval were found. Flucytosine administration may lead to detectable plasma concentrations of 5-fluorouracil and resulting neutropenia, thrombocytopenia, and gastrointestinal mucositis. There is one case report of 5-fluorouracil causing ST segment elevation and chest pain in a 34-year-old woman. This was associated with a decline in ejection fraction to 15 % and in cardiac index to 1.8 L/min/m^2 [97]. Cardiotoxicity occurs in a small percentage of patients treated with 5-fluorouracil and most of these present with ST segment elevation and cardiac ischemia [98]. Given the similar presentation, it is possible that this case represents 5-fluorouracil-induced cardiotoxicity in an ultrasensitive individual.

Echinocandins

Micafungin did not suppress I_{Kr} current in a whole cell patch-clamp assay (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021754s000_PharmR.pdf; accessed 26 March 2014, FDA Pharmacology review, 14 March 2005). Preclinical characterization of the effect of anidulafungin on QT interval was not required. However, ECGs done during clinical development did not suggest an effect on QTc intervals (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021754s000_MedR_P1.pdf; accessed 26 March 2014, FDA Medical review, 18 May 2004). A 41-year-old man developed bradycardia (rate 40 bpm) and severe hypotension (systolic BP 40 mm Hg) about 10 minutes into the first infusion of anidulafungin. The anidulafungin was stopped and the patient was resuscitated; however, there was persistent coma, encephalopathy and hypoxic brain damage. The patient died 13 days after the event and there was no clear explanation of the pathophysiology [99]. No other case reports of cardiotoxicity were found.

Terbinafine

There was no evidence of QT prolongation in a group of 21 subjects who received terbinafine 250 mg/day for 18 days [100]. No studies were found that examined the effect of terbinafine on I_{Kr} function. Also, no reports of cardiac arrhythmias or QT prolongation in animals or humans were located.

Detection and Documentation of TdP Events

When using antifungal azoles, potential cardiotoxicity should always be considered, but since TdP and other types of cardiotoxicity are rare, this risk should not limit their use in most patients. The following strategy is recommended for managing potential QT prolongation involving antifungal azoles: (1) screen the patient's medication list for other drugs with potential to prolong QTc; (2) evaluate medical history for arrhythmias, significant bradycardia, and/or prolonged QTc interval; (3) avoid hypokalemia, and hypomagnesemia; (4) check for potential pharmacokinetic interaction of the azole with other prescribed QT-prolonging drugs; (5) reevaluate the need for concomitant QT-prolonging drugs and consider alternatives; and (6) perform ECG monitoring for high risk patients who are given antifungal azoles concomitantly with the drugs listed in Table 2 or other drugs known to prolong QT. Clinicians should be alert to prolonged QTc from ECG recordings and signs and symptoms of TdP including episodes of syncope or near syncope, ventricular tachycardia, and cardiac arrest. If TdP is documented or suspected, drugs associated with QT prolongation should be discontinued. A guideline for standardized reporting of drug-induced TdP has been developed and this serves as an excellent evaluation tool [101•]. Finally, genetic testing should be considered to identify unrecognized or silent inherited long QT syndrome [6, 8]. In some patients, QT-prolonging drugs may severe to unmask inherited long QT syndrome.

Conclusion

Many antifungal drugs, especially antifungal azoles, rarely cause TdP and carry a risk of sudden death. When using these agents, modifiable risk factors should be considered, and corrected or avoided when possible. The most important modifiable risk factors are hypokalemia, hypomagnesemia, severe bradycardia, and the use of concomitant QT-prolonging drugs. ECG monitoring should be considered when the use of multiple QT-prolonging drugs is unavoidable. If a case of TdP is documented or suspected, genetic testing should be sought since patients with silent long QT syndrome are at risk of future cardiac events. Such patients may be ultrasensitive to the QT-prolonging effects of drugs and medical conditions.

Compliance with Ethics Guidelines

Conflict of Interest DE Nix declares no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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101.• Behr ER, January C, Schulze-Bahr E, Grace AA, Kaab S, Fiszman M, et al. The International Serious Adverse Events Consortium (iSAEC) phenotype standardization project for drug-induced torsades de pointes. Eur Heart J. 2013;34(26):1958–63. *The paper describes a consensus effort to standardize the evaluation and reporting of drug-induced TdP events. The recommendations for the required data for case submissions and extended findings should be considered when documenting any case of drug-related TdP.*