Sinus bradycardia and chronotropic incompetence associated with single-agent itraconazole antifungal therapy: A case report

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Introduction

Adverse cardiac effects are a known, albeit infrequent, complication of azole antifungal drug therapy.[1,2] Most often, cardiotoxicity is the result of drug–drug interactions due to azole inhibition of CYP3A4, but also of CYP2C19 and CYP2C9, leading to increased serum levels of concomitantly administered medications that require hepatic metabolism. Adverse interactions of azole antifungal drugs with digoxin or terfenadine are well known.[1,3–12] Cytochrome P450 inhibition may also result in reduced activity of prodrugs that require hepatic metabolism to be converted to active metabolites.

Apart from the potential impact of altered drug metabolism, azole antifungal agents also exhibit direct pharmacologic actions that may result in adverse cardiac proarrhythmic effects. Most important of these is moderate QT-interval prolongation principally attributed to azole-induced blockade of the rapid component of delayed rectifier potassium current I_{Kr} and possibly the ultrarapid activating component of delayed rectifier potassium current I_{Kur}.[13] In the ventricle, I_{Kr} block may increase the risk of torsades de pointes polymorphic ventricular tachycardia. In the atrium, I_{Kr} and I_{Kur} blockade is expected to result in prolongation of action potential duration.[13,14] The latter effect may be expected to delay onset of intrinsic cellular pacemaker function, resulting in bradycardia.[14,15]

The report presented here describes a case of development of symptomatic sinus bradycardia and chronotropic incompetence in a patient with normal cardiac function being administered oral therapy with the azole antifungal drug itraconazole (ITZ) in the absence of any other cardioactive medications.

KEYWORDS Itraconazole; Bradycardia; Chronotropic incompetence

ABBREVIATIONS **CYP2C19** = cytochrome P450 C19; **CYP2C9** = cytochrome P450 C9; **CYP3A4** = cytochrome P450 3A4; **HERG** = human ether-à-go-go–related gene; **HPLC** = high-pressure liquid chromatography; **I_{Kr}** = rapid component of delayed rectifier potassium current; **I_{Kur}** = ultrarapid activating component of delayed rectifier potassium current; **ITZ** = itraconazole (Heart Rhythm Case Reports 2015;1:6–9)

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Case report

A 43-year-old male recreational runner was referred to the arrhythmia service for evaluation of bradycardia and decreased exercise tolerance. He had been in excellent health but had contracted blastomycosis pneumonia 2 months previously; the mycosis was attributed to his having aspirated contaminated soil during a steeplechase race involving mud pit obstacles. Initial treatment consisted of a 2-week course of amphotericin B, after which he was maintained on ITZ on an outpatient basis. He was not septic and was taking no other medications except for multivitamins. He had no evident immunologic deficiency identified despite thorough evaluation.

The patient became concerned when he noted that his resting heart rate ranged from 40 to 45 bpm (beats per minute), whereas it usually had been 55 to 60 bpm. It also became evident that he was experiencing chronotropic incompetence; his maximum running exercise rate was now approximately 130 bpm when previously he had easily attained heart rates of 170–180 bpm during spontaneous exertion. At the time of recognition of his slow heart rate and exercise limitation, he had been taking ITZ 200 mg orally twice daily for 46 days. His resting heart rate was noted to be in the 40s.

On presentation, the patient's ECG showed sinus bradycardia (40–44 bpm), a previously undocumented leftward frontal axis, and a nonspecific intraventricular conduction disturbance (Figure 1). QT/ QTc intervals were prolonged (496/424 ms) and were longer than recorded on his only ECG recorded 4 years earlier (QT/QTc 386/404 ms; Figure 2). Physical examination revealed an apparently healthy normotensive man. Cardiac tones were normal. Chest examination was positive for right basilar inspiratory rales but otherwise good air entry and no rhonchi. Serum electrolyte measurements on admission were normal except for potassium of 3.3. The hypokalemia resolved with minimal potassium repletion. Cardiac biomarkers, including troponin and N-terminal pro B-type natriuretic peptide (Nt-pro BNP), were within the normal ranges.

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KEY TEACHING POINTS

- Azole antifungal therapy has been associated, albeit infrequently, with cardiotoxicity. Most often, the adverse cardiac effects are the result of drug–drug interactions due to azole inhibition of hepatic metabolism of certain concomitantly administered medications. The result is increased serum levels and potential toxicity of drugs requiring CYP3A4, but also 2C19 and 2C9, metabolism.
- The azole antifungals may also exhibit direct adverse cardiac tachyarrhythmic effects. The most important of these is torsades de pointes ventricular tachycardia due to moderate QT-interval prolongation principally attributed to azole-induced blockade of I_{Kr}.
- Bradycardia is a much less common arrhythmic complication of azole antifungals. However, both sinus bradycardia and chronotropic incompetence may occur and become symptomatic with prolonged exposure to these agents.

Because of the new leftward axis, the subtle intraventricular conduction delay, and prior reports of azole-induced cardiomyopathy, the patient underwent cardiac stress magnetic resonance imaging).[1] Findings revealed normal left ventricular ejection fraction, normal right ventricular ejection fraction, and no evidence of myocardial fibrosis. There was no evidence of stress-induced wall-motion abnormality or diastolic dysfunction. He had negative Lyme immunoglobulin G and immunoglobulin M titers, and his thyroid-stimulating hormone level was normal (1.55 mU/L). His ITZ level measured by high-pressure liquid chromatography (HPLC) was 2.73 μg/mL, and his hydroxy-ITZ level was >3 μg/mL, both above the minimal therapeutic level.

The patient remained clinically stable throughout the hospital visit, with the lowest heart rates in the mid–40 bpm range during waking hours. At 3-month follow-up, he was assessed in the infectious disease clinic, where he continued to report limitation of exercise tolerance that was attributed to symptomatic bradycardia. Antifungal therapy was continued in anticipation of a 6-month treatment course.

Discussion

The principal observation in this report was the apparent occurrence of both bradycardia and symptomatic chronotropic incompetence in a patient being treated with ITZ. In the absence of any other cardioactive drug or underlying structural heart disease in the patient, the findings strongly suggest a rare direct ITZ adverse electrophysiologic effect.

Arrhythmic complications are known potential complications of azole antifungal drug treatment.[1,3–12,16] For the most part, however, the basis for azole-induced proarrhythmia is an adverse drug–drug metabolic interaction (typically due to azole inhibition of the cytochrome P450 hepatic metabolic pathway) rather than a direct cellular electrophysiologic effect. In addition, tachyarrhythmias, particularly torsades de pointes ventricular

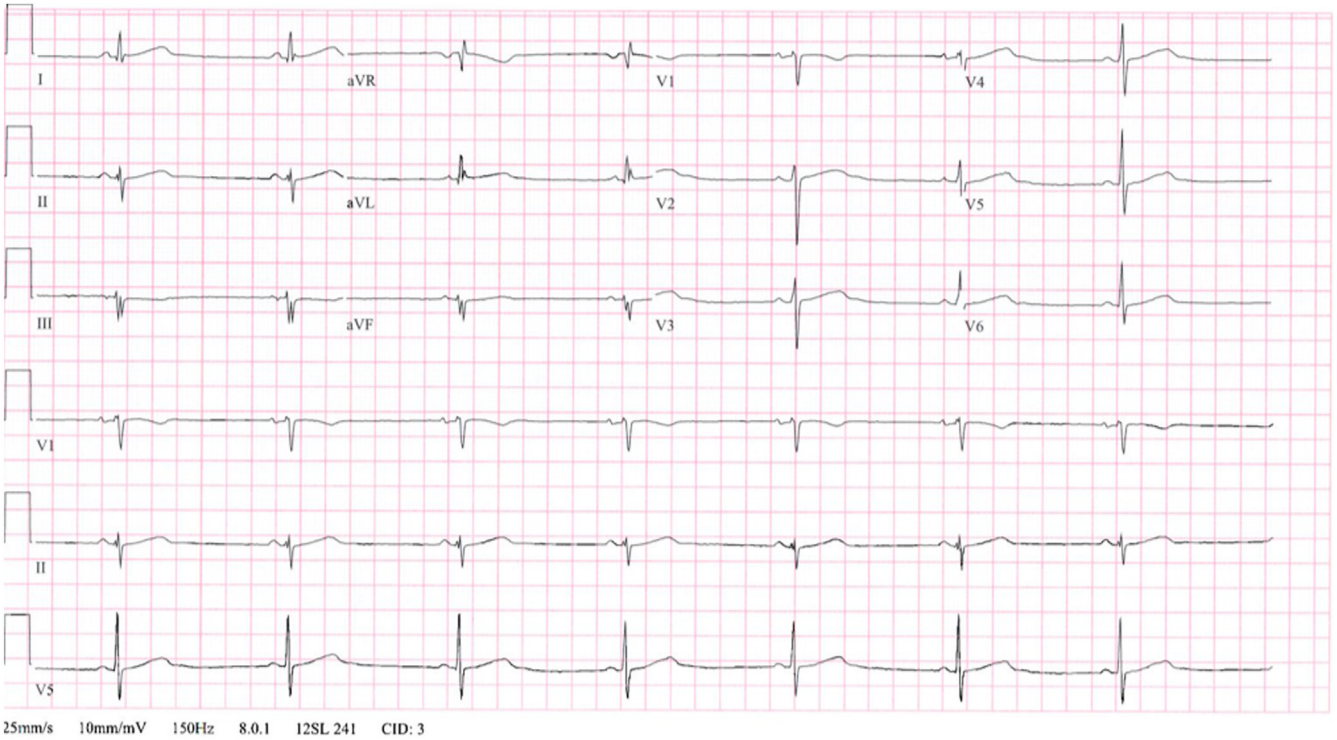

Figure 1 Twelve-lead ECG obtained when the patient presented with complaints of fatigue and exertional limitation. The tracing reveals sinus rhythm at 44 bpm. A leftward axis is present and is new since his only ECG recorded 4 years earlier (see Figure 2). QT/QTc is prolonged (496/424 ms).

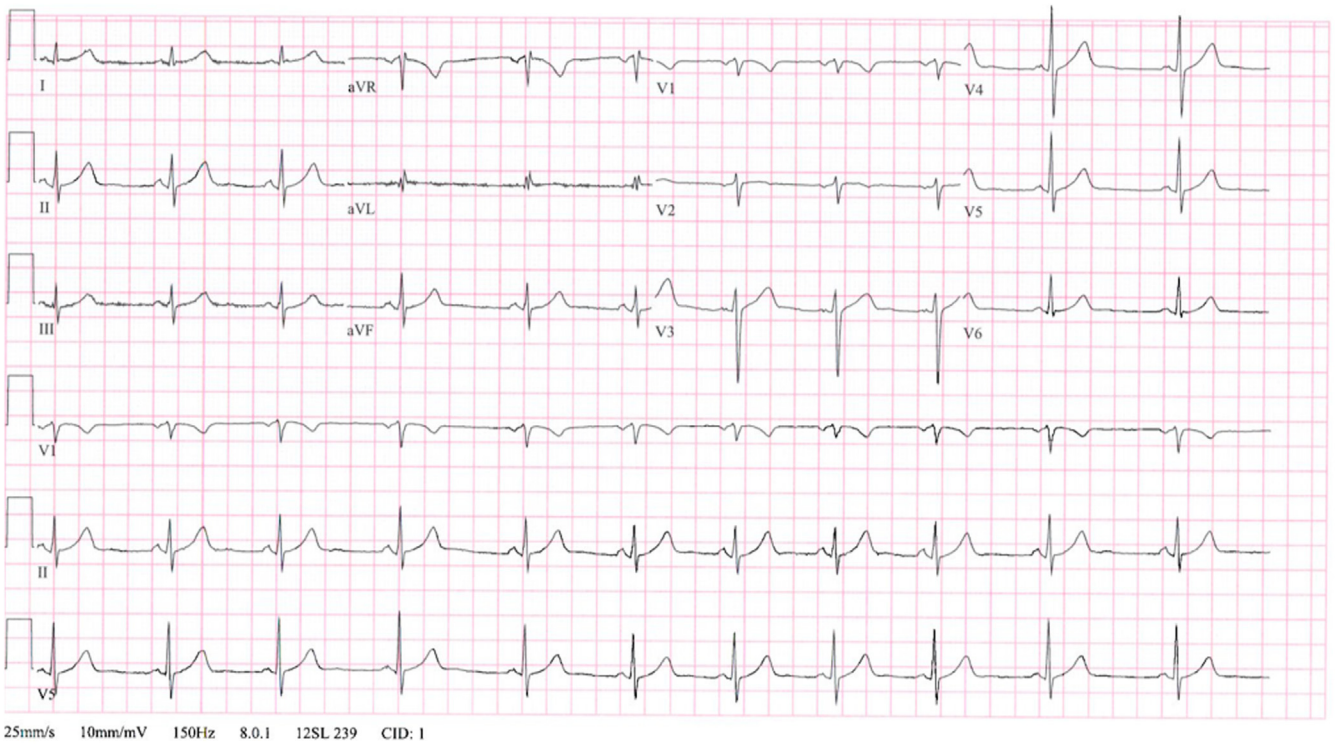

Figure 2 Twelve-lead ECG obtained 4 years before that shown in Figure 1 as part of a routine physical examination. This is the patient's only prior ECG. At the time he was taking no cardioactive drugs. The tracing is normal, showing sinus rhythm with sinus arrhythmia and a heart rate averaging 65 bpm. QT/QTc is normal (386/404 ms).

tachycardia, have been of greatest concern,[1,9,10] whereas bradyarrhythmias have attracted less attention.[7,8,11,12,16]

As a class, the azole antifungals are believed to exhibit cellular electrophysiologic effects similar to those reported for the prototypical agent ketoconazole. In this regard, Dumaine et al,[13] using heterologously expressed channels, observed that both HERG (human ether-à-go-go–related gene) associated with I_{Kr} as well as Kv1.5 channel associated with I_{Kur} were suppressed by ketoconazole in the absence of other agents. The overall potassium blockade effect would be expected to prolong ventricular refractoriness and lead to QT prolongation. HERG is also expressed in atrial cells. Consequently, I_{Kr} and I_{Kur} suppression may prolong atrial action potential duration and refractoriness and delay onset of the pacemaker current I_f in sinoatrial cells, with bradycardia as the result. Whether conduction system disease, such as the new leftward axis deviation observed in our patient, can similarly be attributed to azole-triggered electrophysiologic effects is less certain.

In the clinical setting, bradycardia has been reported with ITZ therapy in a comparative trial with voriconazole[16]; however, the severity of bradycardia was not noted, and the potential contribution of concomitant medications to triggering the bradyarrhythmia was unclear. On the other hand, bradycardia has been associated with voriconazole.[11,16] However, in a report by Perbet et al[11] incorporating 3 intensive care unit patients, all 3 patients were very ill, and at least 1 of the 3 patients likely was the recipient of a number of other confounding drugs. Severe fungemia alone has also been associated with bradycardia,[17] thereby complicating interpretation of drug effects in severely ill individuals.

Currently, there is no consensus regarding the upper bound of the therapeutic level for ITZ.[18,19] One toxicodynamic study showed that patients on ITZ monotherapy whose levels were >17.1 μg/mL by bioassay tended to be at higher risk for adverse effects.[17] Bioassay measurements combine the activity of ITZ and its pharmacologically similar metabolite hydroxy-ITZ into 1 measurement, whereas HPLC directly measures the concentration of each compound. Results obtained by the 2 measurement techniques are not directly comparable, although a study correlating the methods suggested that the bioassay generates measurements ~7-fold higher than those obtained by HPLC.[18] Because our patient's ITZ level by HPLC was 2.73 μg/mL, which roughly equates to an estimated level of 19 μg/mL by bioassay, he would be in a higher risk category for cardiac toxicity. On the other hand, some of the adverse effects of azoles seem not to be dose related,[9,11] suggesting that these agents may be associated with unpredictable idiosyncratic outcomes.

Attributing the bradycardia and chronotropic incompetence in this patient to direct effects of ITZ is limited by several factors. First, as noted earlier, fungemia alone has been associated with bradycardia and thereby could have contributed to the clinical picture. However, unlike reported cases of bradycardia in patients with severe fungal infections, our patient never exhibited a septic picture, and his systemic symptoms were mild and reversed with minimal intervention. Second, although moderate resting bradycardia has

persisted, repeat assessment of chronotropic responsiveness has not been undertaken. Consequently, the persistence of any drug effect on chronotropic response is not conclusively proven. Finally, and perhaps most importantly in athletic individuals, is an inherent proclivity for low heart rates because of their athletic participation and high degree of aerobic conditioning. However, in our case the patient was very attuned to his exercise tolerance and had not previously experienced the exercise heart rate limitations that occurred after initiation of ITZ.

Given the timing of the onset of bradycardia and chronotropic incompetence in our patient with respect to initiation of ITZ treatment and in the absence of either other cardioactive drugs or underlying structural heart disease, we conclude that QT-interval prolongation, the resting bradycardia, and the symptomatic chronotropic incompetence were due to the direct electrophysiologic effects of ITZ therapy.

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