

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.

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.

KEYWORDS Itraconazole; Bradycardia; Chronotropic incompetence

ABBREVIATIONS CYP2C19 = cytochrome P450 C19; CYP2C9 = cytochrome P450 C9; CYP3A4 = cytochrome P450 3A4; HERG = human ether-à-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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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 $\mu\text{g/mL}$, and his hydroxy-ITZ level was $>3 \mu\text{g/mL}$, 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

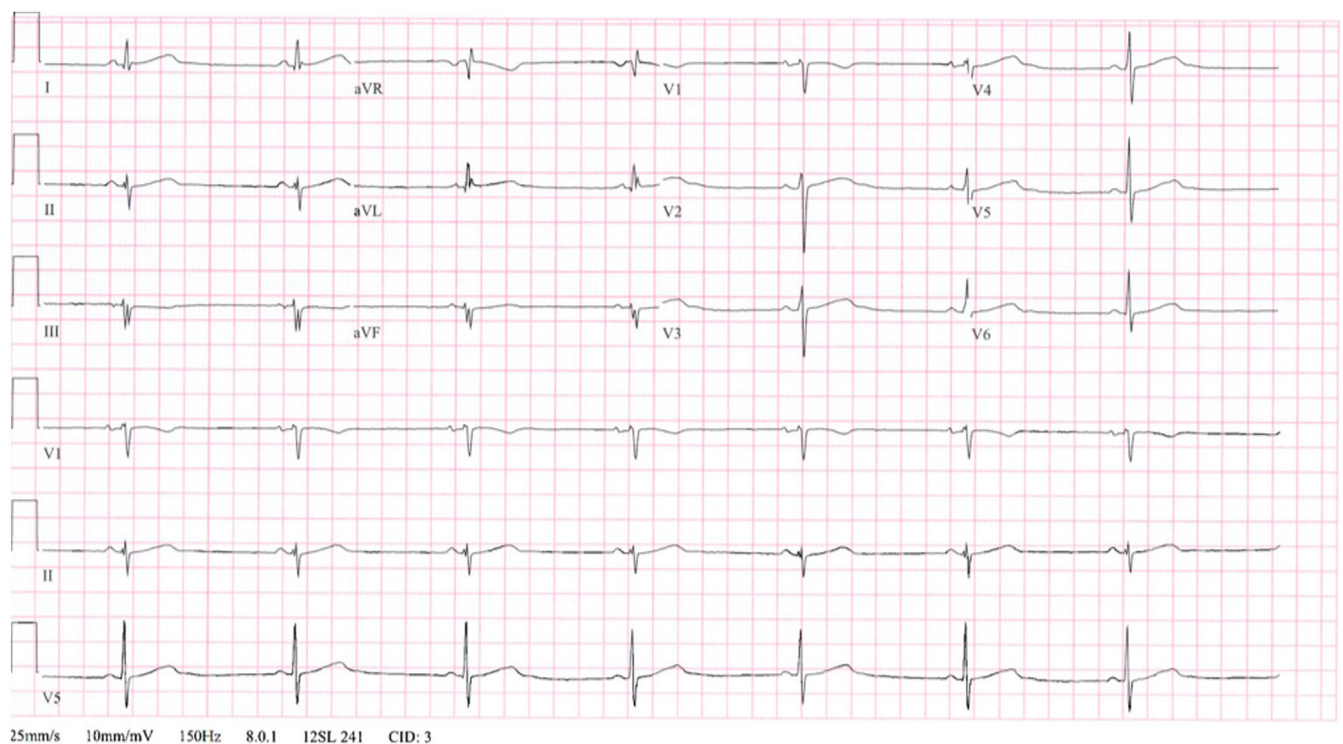


Figure 1 Twelve-lead ECG obtained when the patient presented with complaints of fatigue and exertional limitation. The tracing reveals sinus rhythm at 44 bpm. A leftward axis is present and is new since his only ECG recorded 4 years earlier (see Figure 2). QT/QTc is prolonged (496/424 ms).

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