CASE REPORT

Cardiotoxicity with Itraconazole

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SUMMARY

Itraconazole is a commonly used antifungal drug. In addition to commonly described adverse effects, there have been few reports of heart failure with its use. We present two cases that developed acute systolic heart failure with Itraconazole use. A man in his early 30s was admitted with worsening leg swelling and dyspnoea on exertion. He had been on Itraconazole for blastomycosis skin ulcer. His ejection fraction (EF) was found to be 10%–15%. Another man in his 50s was admitted with similar symptoms; his EF was 40%–45%. He had been on Itraconazole for forearm cellulitis. No other aetiology was identified in both patients despite extensive work-up including cardiac catheterisation. Itraconazole was stopped in both the cases. Our first patient did not improve even months after cessation of therapy and was referred for heart transplant. Our second patient improved after a few weeks, and his ejection fraction had improved on repeat testing.

BACKGROUND

Itraconazole is a commonly used agent for many fungal infections especially in the midwestern USA, due to the high prevalence of histoplasma and blastomycosis infections. In addition to the usual common side effects of the azoles class of drugs, Itraconazole has been associated with some potentially serious cardiac side effects including congestive heart failure (CHF). Patients on Itraconazole therapy should be carefully monitored for and warned of symptoms of CHF. Benefits should strongly outweigh the risks before considering starting Itraconazole in patients with pre-existing left ventricular dysfunction. We present two cases of systolic CHF which were attributed to Itraconazole use.

CASE PRESENTATION**Case 1**

A 31-year-old man was admitted to the hospital for progressively worsening dyspnoea on exertion for 2 months. He had been on Itraconazole therapy for 6 months for cutaneous blastomycosis. He reported orthopnoea, bilateral lower leg swelling and significant weight gain. He denied any chest pain, palpitations, past cardiac problems and any recent viral illness or rashes. There was no family history of heart disease. On examination, apart from low arterial oxygen saturation (Sao_2), the rest of his vital signs were stable. He had significant elevation of jugular venous pressure. On chest auscultation, there were crackles bilaterally up to mid-lung fields. There was 2+ pitting oedema of bilateral lower extremities and a healing ulcer on the left leg.

Basic laboratory parameters including cardiac markers were within normal limits. NT-proBNP level was 4603 pg/mL (normal 0–125 pg/mL). Echocardiogram showed an ejection fraction (EF) of 10%–15%. Intravenous diuretics significantly improved his symptoms. Cardiac catheterisation revealed normal coronaries, but elevated pulmonary capillary wedge pressure of 22 mm Hg. With no clear aetiology identified that would cause heart failure, Itraconazole was the likely culprit and hence stopped.

Case 2

A 64-year-old man with history of rheumatoid arthritis, and cellulitis secondary to histoplasmosis was admitted to the hospital for complaints of shortness of breath along with bilateral lower extremity swelling and pain. He had been on Itraconazole for 3 months for forearm cellulitis, which was biopsy proven to be caused by histoplasma. His dyspnoea had been worsening over the last few weeks. On examination, his vital signs were stable. Heart sounds were irregularly irregular, and there was reduced air entry at bilateral lung bases. Lower extremities had pitting oedema up to the knees.

Basic blood work including complete blood count, serum chemistries and cardiac biomarkers were within normal limits. ECG showed atrial fibrillation with ventricular rate of 105/min. Echocardiogram showed reduced EF of 45%. He had a negative stress test about 6 months ago that showed normal EF. A CT chest scan done to rule out pulmonary embolism showed moderate bilateral pleural effusions and features of pulmonary vascular congestion. Intravenous diuretics helped relieve his symptoms. Thoracentesis revealed transudative pleural effusion. Cardiac catheterisation done to rule out ischaemia showed normal coronaries. Itraconazole was stopped as his cellulitis had resolved.

OUTCOME AND FOLLOW-UP**Case 1**

The patient required diuretic therapy for control of his symptoms. Repeat echocardiogram after 3 months again showed very low EF. Hence automatic implantable defibrillator (AICD) was placed, and the patient was referred for cardiac transplant evaluation. Unfortunately, he suffered from a sudden cardiac arrest at home. When the emergency medical team arrived, the initial rhythm recorded was asystole. His family politely denied the autopsy request.

Case 2

The patient's symptoms improved significantly, and we were able to taper off diuretics in a few weeks.

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Follow-up echocardiogram 6 months after stopping itraconazole showed an EF of 55%.

DISCUSSION

Itraconazole, available under the brand name Sporanox in USA, is a commonly used antifungal agent for infections like aspergillosis, blastomycosis, histoplasmosis and onychomycosis. Like other azoles, it inhibits the fungal-mediated synthesis of ergosterol, via inhibition of lanosterol 14-demethylase. Common side effects associated with Itraconazole include nausea, vomiting, diarrhoea and transaminitis.

Cardiac toxicity is an uncommon side effect of antifungal medications. Earlier amphotericin B was the only one described with cardiac side effects such as arrhythmias mainly due to electrolyte disturbances. In the recent past, there has been increased recognition of cardiotoxic effects of Itraconazole. Hauben and Hung,¹ in their review of the US Food and Drug Administration Adverse Event Reporting System database, found CHF-related events not to be a class effect of all antifungal drugs, but only Itraconazole. From 1992 to 2001, 58 cases of heart failure probably associated with the use of Itraconazole were reported by Ahmad *et al.*² There have been few more reported cases in literature since then.

The exact mechanism of the cardiac side effects remains unclear, but some recent data suggest mitochondrial dysfunction.

Cleary *et al.*³ described mitochondrial toxicity as the cause of negative inotropic effects in animal models. Qu *et al.*⁴ in their study found a direct effect leading to negative inotropic effect, decreased heart rate and coronary flow but no mitochondrial dysfunction. However, both the studies and reported cases describe negative inotropic effect. Most data suggest increased risks with doses greater than 400 mg/day. Hence, careful dosing and monitoring of drug levels becomes very important.

Almost all individual case reports describe improvement in symptoms of CHF and improvement in EF after cessation of therapy, except the series presented by Ahmad *et al.* In their report, 28 out of 58 patients were admitted to the hospital of whom 13 eventually died.² We could not find any description of whether the EF had improved in any of those patients. One of our patients did not show improvement in EF even after a year. Hence, stopping the therapy does not necessarily mean resolution of cardiac dysfunction.

These two cases do highlight the importance of monitoring symptoms of heart failure in patients who are started on Itraconazole therapy. If possible, it should be avoided in patients who have pre-existing heart disease or, at least, risks and benefits should be strongly weighed and explained to the patients.

Contributors VP took care of both patients as the attending physician on the case. VP edited the case write-up and the discussion. HR carried out the literature review and drafted the initial case write-up.

Competing interests None declared.

Patient consent Obtained.

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Learning points

- ▶ Itraconazole can cause acute congestive heart failure (CHF) or worsening of pre-existing ventricular dysfunction. Monitor patients closely and instruct them about symptoms of heart failure; they should stop the medicine if any symptoms occur.
- ▶ Itraconazole should be avoided in patients with pre-existing heart failure unless benefits clearly outweigh the risks.
- ▶ Itraconazole levels should be monitored regularly.
- ▶ There is a good likelihood for improvement in CHF after cessation of therapy, but not always.

REFERENCES

- 1 Hauben M, Hung EY. A quantitative analysis of the spontaneous reporting of congestive heart failure-related adverse events with systemic anti-fungal drugs. *J Clin Pharmacol* 2013;53:762–72.
- 2 Ahmad SR, Singer SJ, Leissa BG. Congestive heart failure associated with itraconazole. *Lancet* 2001;357:1766–7.
- 3 Cleary JD, Stover KR, Farley J, *et al.* Cardiac toxicity of azole antifungals. *Pharmacology & Pharmacy* 2013;04:362–8.
- 4 Qu Y, Fang M, Gao B, *et al.* Itraconazole decreases left ventricular contractility in isolated rabbit heart: mechanism of action. *Toxicol Appl Pharmacol* 2013;268:113–22.

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