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The Many Faces of Itraconazole Cardiac Toxicity

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Abstract

Itraconazole is well known for carrying a black-box warning for new or worsening congestive heart failure. Single cases of other cardiac- and fluid-related disturbances have been reported periodically since its issuance. We describe a large cohort of patients on itraconazole experiencing a breadth of cardiac- and fluid-related toxicities, ranging from new-onset hypertension to cardiac arrest. A retrospective, single-center, large case series at a large tertiary medical center was conducted. Patients with itraconazole and cardiac toxicity—including hypertension, cardiomyopathy, reduced ejection fraction, and edema—in medical record between January 1, 1999, and May 21, 2019, were identified and assigned a Naranjo score; 31 patients were included with a Naranjo score of 5 or higher. There were slightly more male subjects than female subjects, average age was 66, and all subjects were Caucasian. Median time until presentation of adverse effects was 4 weeks (range: 0.3 to 104 weeks). Most common symptom was edema (74% of patients), followed by heart failure without and with preserved ejection fraction (19.4% and 22.6% of patients, respectively). Worsening or new hypertension was also common (25.8% of patients). Rarer were pulmonary edema, pericardial effusion, and cardiac arrest that occurred in 1 patient. In most cases, clinicians stopped itraconazole (74%) or decreased itraconazole dose (19%), resulting in improvement or resolution of symptoms. In 4 cases, the adverse effect did not resolve. Itraconazole can cause a range of possible serious cardiac and fluid-associated adverse events. Dose decrease or cessation usually resulted in symptomatic improvement or reversal.

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Itraconazole is a triazole antifungal commonly used to treat serious fungal infections. In 2001, the Food and Drug Administration (FDA) issued a black-box warning to itraconazole labeling about the risk of new or exacerbated congestive heart failure (CHF).[1] The FDA warning stated that itraconazole should not be used for onychomycosis in patients with ventricular dysfunction because of negative inotrope activity seen in healthy human volunteers and dogs.[2] Although not fully understood, proposed mechanisms of this effect include mitochondrial toxicity.[3] Following the initial publication describing 58 cases of itraconazole-associated cardiac failure,[1] related cases have periodically been reported.[4-7] Particularly concerning are cases of CHF in the setting of no previous cardiac risk factors.[5,6] Although CHF is the most commonly described form of cardiotoxicity, reports generally consisting of 1 to 2 patients suggest the scope of toxicity spans more widely. Case reports of cardiovascular (CV) or fluid disorders attributed to itraconazole include peripheral edema,[8] polyuria,[9] hypertension,[10-12] and cardiac arrest:[13] the latter typically involving concomitant QT-prolonging medications.

We sought to describe the patients seen at our institution in the last 2 decades with widely defined CV- or fluid-related adverse effects that we determined to be probably systematically related to the use of itraconazole and describe their outcomes.

METHODS

This single-center retrospective, descriptive study was conducted at Mayo Clinic Rochester. Institutional review board approval was obtained. Charts of all adult patients with itraconazole orders were queried between January 1, 1999, and May 21, 2019, using the Mayo

Clinic Unified Data Platform.[14] Patients without research authorization in Minnesota were excluded. Clinical notes were searched for terms *itraconazole and hypertension*, *cardiomyopathy*, *reduced ejection fraction*, or *edema*. Identified patients were reviewed, and the Naranjo adverse drug event (ADE) scoring tool[15] was used to rate the likelihood of an itraconazole-associated ADE by 2 clinical pharmacists reviewing cases independently. If the pharmacist was unable to determine a score clearly, an infectious diseases physician provided input. Patients with Naranjo scores ≥ 5 (probable or definite ADE) were included. Patients scoring <5 (possible or doubtful ADE) were excluded. Data collected included patient age, sex, race, itraconazole indication, itraconazole- dosing history, itraconazole start date per prescription record and provider documentation for internal and the latter only for external initiation, itraconazole formulation at time of CV toxicity, clinician response, CV-toxicity resolution, itraconazole/hydroxy-itraconazole level, cardiac comorbidities, and pharmacogenomics results. Predefined cardiac comorbidities included cardiac arrhythmias, established coronary artery disease, cardiomyopathy, diabetes, hypertension, or hyperlipidemia. Concomitant medications were screened for potential alternative causes and Naranjo points assigned accordingly. CV toxicity was defined as complete resolution: no further signs, symptoms, or test results indicating adverse effect; partial resolution: ≥ 1 sign, symptom, or test result indicating adverse effect and severity has improved or number of symptoms decreased since presentation; no resolution: signs, symptoms, and/or test results continue at same frequency and severity or worsen.

Serum drug levels were performed in the majority of patients at steady state (1 to 3 weeks following initiation of drug or change in dose). Itraconazole and its primary active metabolite— hydroxy-itraconazole—levels were assessed on site. Drug assay was performed by liquid chromatography-tandem mass spectrometry from a single serum sample. Laboratory reference suggests goals of >0.5 μg/mL for a localized infection and >1 μg/mL for systemic infections, with no defined upper limit. Results of each individual component were available via the electronic medical record laboratory section. Itraconazole and hydroxy-itraconazole results were summed and compared with the total to the aforementioned goal values. We reported the highest sum of itraconazole and hydroxy-itraconazole during a single assay recorded for each patient within the study time frame. This result was usually the serum level at the time of occurrence of the ADE.

RESULTS

Of the initial 69 patients identified with itraconazole and a cardiac- or fluid-related ADE, 31 cases that scored ≥ 5 by Naranjo scale were included. Physician input on scoring was obtained on 1 of the included cases and 3 of the excluded cases. There were slightly more men than women, with an average age of 66, and all were Caucasian. The most common cardiac comorbidities were hypertension (22%) and cardiac arrhythmia (25%), whereas only 1 patient had baseline cardiomyopathy. The most common itraconazole indication was *Histoplasmosis* infection (48.4%) with pulmonary source (51.6%). Disseminated fungal infections were also frequent. In only 1 case was itraconazole used for prophylaxis (Table 1). The average total serum itraconazole level was 5.2 μg/mL (range: 1.8 to 11.7 μg/mL).

The median time from itraconazole initiation until adverse effect presentation was 4 weeks (range: 0.3 to 104 weeks). The most common symptom was edema in 74% of patients, followed by heart failure with and without preserved ejection fraction (HFpEF and HFrEF, respectively) in just under a quarter of patients each. Worsening or new hypertension was present in 25.8% of patients. Rarer, but notable, were pulmonary edema and pericardial effusion; cardiac arrest occurred in 1 patient (Table 2). Most patients experienced more than 1 ADE, and, typically, these presented simultaneously.

In most cases, clinicians stopped itraconazole (74%) or decreased itraconazole dose (19%) in response to perceived itraconazole toxicity. Complete resolution occurred in just over half the patients (54%) and partial resolution in 30%. In the cases with partial resolution, 20% of the time the clinician took an additional action in an attempt to resolve, most commonly discontinuing itraconazole after the dose had first been decreased. In 4 cases (12.9%), the identified toxicity did not

TABLE 1. Patient Characteristics

Characteristic	Total (N=31) N (%)
Sex, Male	17 (54.8)
Age, median (IQR), years	66 (56, 70)
Race	
Caucasian	31 (100)
Cardiovascular comorbidities	
Cardiac arrhythmia	8 (25.8)
Cardiomyopathy	1 (3.2)
Coronary artery disease	5 (16.1)
Hypertension	7 (22.6)
Dyslipidemia	3 (9.7)
Indication	
Pulmonary	16 (51.6)
Disseminated	12 (38.7)
Tenosynovitis	2 (6.5)
Prophylaxis	1 (3.2)
Organism	
Histoplasma	15 (48.4)
Aspergillus	2 (6.5)
Coccidioides	3 (9.7)
Blastomyces	5 (16.1)
Prophylaxis	1 (3.2)
Cryptococcus	1 (3.2)
Other Fungal NOS	4 (12.9)
Naranjo Score, median (range) points	7 (5-9)

IQR = interquartile range; NOS = not otherwise specified.

resolve. Half the HFpEF cases resolved partially, and half resolved fully. For HFrEF, 2 patients had no resolution, 1 had partial resolution, and 3 had complete resolution. A summary of the 31 cases is presented in Table 3.

We describe below 3 cases of heightened interest. Patient 1 demonstrates a combination of severe, concerning cardiac toxicities occurring at a moderate serum itraconazole level. Patient 7 experienced serious cardiac toxicity in the setting of elevated itraconazole levels, possibly related to her pharmacogenomic (CYP450) genotype. Patient 25 experienced dose-dependent nocturia, an effect not previously described in the literature.

Patient 1

A 70-year-old man from Minnesota, with a history of coronary artery disease requiring coronary artery bypass surgery in 2010 and pulmonary sarcoidosis diagnosed in 1996, was hospitalized for acute hypoxic respiratory failure. Bronchoscopy with transbronchial biopsy showed necrotizing granuloma and fungal elements consistent with *Histoplasma capsulatum*. *Histoplasma* urinary antigen results were positive. He started itraconazole liquid 200 mg every 8 hours for 3 days, followed by 200 mg orally every 12 hours. Five weeks later, the total serum itraconazole level was 3.1 μg/mL.

Six weeks later, he was hospitalized with progressive shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, bilateral lower-limb swelling, and N-terminal-pro brain natriuretic hormone of 6066 pg/mL. A transthoracic echo revealed severe right-ventricular enlargement with moderate to severe decrease in systolic function, severely dilated inferior vena cava, and mild tricuspid regurgitation. Troponins were negative, whereas electrocardiogram revealed new evidence of prolonged QT interval and multifocal atrial tachycardia.

Itraconazole was transitioned to voriconazole and later fluconazole for 1 year. Two

TABLE 2. Summary of CV Toxicity Characteristics[a]

Characteristic	Total (N=31) N (%)
CV toxicity type	
CHF with reduced EF	6 (19.4)
CHF with preserved EF	7 (22.6)
Hypertension	8 (25.8)
Edema	23 (74.2)
Pericardial effusion	1 (3.2)
Other	8 (25.8)
Clinician initial action	
Continue itraconazole regimen	2 (4.5)
Discontinue itraconazole	23 (74.2)
Modify itraconazole dose	6 (19.4)
Outcome	
Complete resolution	17 (54.8)
Partial resolution	9 (29)
No resolution	4 (12.9)
Unknown	1 (3.2)
Clinician subsequent action taken	
Yes	6 (19.4)
No	26 (80.6)

[a]Percentages add up to >100%, as many patients had ≥1 CV toxicity.

CV = cardiovascular; CHF = congestive heart failure; EF = ejection fraction.

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TABLE 3. Descriptions of Patient Cases

ID	Age	Sex	CV comorbidities[b]	ITRA indication	CV toxicity type	Naranjo Score	Time to ADE (weeks)	ITRA oral dose[c]	Formulation	ITRA Load[d]	ITRA + H-ITRA level[e] (μg/mL)	Clinician action Regarding ITRA	Resolution
1	70	M	3,5	Pulmonary histoplasmosis	right heart failure, edema	9	6	200 mg BID	capsule	Yes	2	Discontinue	partial
2	67	M		Disseminated histoplasmosis	HTN	8	2	200 mg BID	capsule	Yes	2.9	Discontinue	complete
3	33	M		Disseminated Blastomyces	pleural effusions, pulmonary edema, SOB	8	8	Unknown	liquid	Unknown	6.2	Discontinue	unknown
4	65	M		Pulmonary histoplasmosis	HFpEF, edema	8	2	200 mg BID	liquid	Yes	11.5	Modify dose	complete
5	84	M	3	Pulmonary histoplasmosis and Blastomyces	HTN	8	5	200 mg BID	capsule	Yes	4.3	Discontinue	partial
6	77	M		Pulmonary histoplasmosis	edema, pleural effusion	8	8	200 mg BID	capsule	Unknown	10.1	Discontinue	complete
7	52	F	5	Pulmonary Blastomyces	HTN, edema, hypokalemia, and metabolic acidosis	8	7	100 mg BID	capsule	Yes	7.8	Discontinue	complete
8	68	F	1	Pulmonary Aspergillus	HFpEF, HTN, edema	7	8	200 mg BID	capsule	No	4.8	Modify dose	partial
9	70	F		Pisseminated histoplasmosis	HTN, edema	7	34	200 mg BID	capsule	No	5.9	Discontinue	complete
10	65	M	1,2	Pisseminated Blastomyces	HFpEF, edema, pulmonary edema	7	3	200 mg BID	capsule	Yes	4.8	Discontinue	complete
11	66	F	1	Pulmonary (NOS)	HFpEF, edema	7	1	200 mg BID	capsule	Yes	5.6	Discontinue	complete
12	72	F	1,5,6	Pulmonary Aspergillus	HFpEF, edema	7	3.5	200 mg BID	capsule	No	-	Discontinue	complete
13	69	M	1,6	Penosynovitis (NOS)	HFrEF, edema	7	3	200 mg BID	capsule	No	4.5	Discontinue	complete
14	66	F		Pisseminated Coccidioides	edema	7	1	200 mg BID	capsule	Yes	3.1	Discontinue	complete
15	50	M		Pulmonary histoplasmosis	edema, SOB	7	1.5	200 mg BID	capsule	No	5.9	Discontinue	complete
16	53	F	3,6	Disseminated histoplasmosis	HFrEF, edema	7	4	Unknown	unknown	Unknown	2.3	Discontinue	no resolution
17	63	M		Prophylaxis	HFrEF, edema	7	69	300 mg BID	capsule	Yes	2.5	Discontinue	complete
18	71	F	5	Pulmonary histoplasmosis	HTN, edema	7	4	200 mg BID	capsule	No	5.6	Discontinue	partial
19	57	F		Pulmonary histoplasmosis	edema	6	3	200 mg BID	capsule	Yes	7.5	Continue regimen	no resolution
20	73	M	5	Pulmonary Crytococcus	HFrEF	6	104	200 mg BID	capsule	No	-	Continue regimen	no resolution
21	50	F	1	Pulmonary Coccidioides	edema	6	1	200 mg BID	capsule	Yes	3	Discontinue	complete
22	55	F	1	Disseminated histoplasmosis	HTN, pericardial effusion	6	24	200 mg BID	capsule	Yes	4.3	Modify dose	partial
23	54	M	3	Pulmonary histoplasmosis	edema	6	0.3	200 mg BID	capsule	Yes	-	Discontinue	complete
24	69	M	5	Pulmonary (NOS)	HTN	6	unknown	Unknown	unknown	Unknown	-	Discontinue	complete
25	63	M		Disseminated Blastomyces	edema, nocturia	6	67	200 mg BID	liquid	No	3.5	Modify dose	partial
26	66	F		Pulmonary histoplasmosis	HFrEF	6	4	200 mg QD	liquid	No	2.9	Discontinue	partial
27	73	F	3	Disseminated histoplasmosis	edema	6	104	200 mg BID	capsule	Yes	6.8	Modify dose	no resolution
28	70	M		Disseminated Blastomyces	HFpEF, edema	5	2	200 mg BID	capsule	No	-	Discontinue	partial

Continued on next page

TABLE 3. Continued

ID	Age	Sex	CV comorbidities[b]	ITRA indication	CV toxicity type	Naranjo Score	Time to ADE (weeks)	ITRA oral dose[c]	Formulation	ITRA Load[d]	ITRA + H-ITRA level[e] (μg/mL)	Clinician action Regarding ITRA	Resolution
29	64	M	5	Disseminated Coccidioides	edema	5	2.5	400 mg BID	capsule	Yes	4.8	Modify dose	partial
30	60	F	1	Tenosynovitis histoplasmosis	HFrEF, cardiac arrest	5	30	100 mg BID	liquid	No	11.7	Discontinue	complete
31	21	M		Disseminated histoplasmosis	edema	5	3	300 mg BID	liquid	Yes	1.8	Discontinue	complete

[b]Defined risk factors include arrhythmia = 1, cardiomyopathy = 2, coronary artery disease = 3, diabetes = 4, hypertension = 5, or hyperlipidemia = 6.
[c]Dose at time of adverse drug event.
[d]200 mg PO TID for at least 3 days at beginning of therapy.
[e]Highest total (itraconazole + hydroxyitraconazole) level recorded.
ADE = adverse drug event; BID = twice daily; CV = cardiovascular; HFrEF = heart failure with reduced ejection fraction (left-ventricular ejection fraction ≤40%); H-ITRA = hydroxy-itraconazole; HTN = hypertension; ID = identification; NOS = not otherwise specified; ITRA = itraconazole; SOB = shortness of breath.

years later, a repeat transthoracic echo showed improvement in the right-ventricular size but remained mildly dilated.

Patient 7

A 52-year-old former nurse from Minnesota with a history of hypertension presented with muscle weakness, bone pain, and diarrhea following a trip to Florida. Chest computed tomography demonstrated left lower-lobe cavitary lesion and right upper-lobe ground-glass nodule. *Blastomyces* urine antigen was low positive (0.35 ng/mL). Itraconazole (capsule formulation), 200 mg every 8 hours for 3 days, followed by 200 mg twice daily, was initiated for possible blastomycosis. Ten days later, the combined itraconazole/hydroxyitraconazole serum level was 4.8 μg/mL. The itraconazole dose was decreased to 200 mg in the morning and 100 in the evening, resulting in a total itraconazole serum level of 7.8 μg/mL. The itraconazole dose was further reduced to 100 mg, twice daily.

One month later, the patient reported increased blood pressure, new-onset dyspnea, slight swelling in her hands and feet, mouth ulcers, and poor appetite. Repeat total itraconazole level was 6.5 μg/mL. The itraconazole dose was further decreased to 100 mg daily. Shortness of breath progressed to dyspnea with minimal exertion and difficulty speaking. She reported chest pain, reported to emergency care, and was found to be in respiratory acidosis and hypokalemic, with serum potassium 2.8 mmol/L without known cause. Itraconazole was stopped, and subsequently her blood-pressure control improved, but dyspnea symptoms waxed and waned. Seventeen days later, her total itraconazole serum level was 1.4 μg/mL. Several months later, pharmacogenomics testing revealed CYP3A4 genotype*1/*22, which is associated with reduced 3A4 function. Approximately 2 years later, she was newly diagnosed with HFpEF at an outside institution.

Patient 25

A 63-year-old man from Wisconsin, with a history of pulmonary sarcoidosis, hyperlipidemia, benign prostate hypertrophy, and mild idiopathic low CD4, presented with a history of recurrent blastomycosis treated with itraconazole for 2 years, dosed at 100 mg twice daily. He had a pulmonary relapse of

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blastomycosis and was retreated with itraconazole capsules 200 mg twice daily, which now was associated with frequent nocturia of 4 to 5 times nightly. Because of the marked nocturia, the itraconazole was decreased to 100 mg twice daily. With this dose reduction, nocturia improved to 1 to 2 times per night. Total serum itraconazole on this dose was 3.5 μg/mL. His history was unremarkable for heart failure, fluid retention, or peripheral edema. Following completion of 18 months' treatment dosing, the itraconazole dose was decreased to 100 mg, once daily, for lifelong secondary prophylaxis, which led to a decrease in nocturia to 1 time nightly. Nocturia completely resolved with itraconazole 100 mg, 3 times weekly. The patient was switched to fluconazole for secondary prophylaxis in early 2019.

DISCUSSION

This study is the largest of its kind to detail itraconazole-related toxicity comprehensively at a single center since the FDA warning was issued nearly 20 years ago. Although the notion of cardiac- and fluid-related toxicity associated with itraconazole is known, the variety in patient presentations and specific sequelae were significant findings. Although some patients experience classic reduced ejection fraction, others demonstrated preserved ejection fraction. A possible mechanism is itraconazole damage to myofibroblasts or mitochondrial dysfunction, as seen with anthracycline cardiotoxicity.[16,17] In addition, fluid retention and hypertension, as experienced by Patient 25, may be related to mineralocorticoid excess. Thompson et al. have postulated that itraconazole inhibition of 11β-hydroxysteroid dehydrogenase 2 may lead to this effect.[18] In a few cases, clinicians did not recognize itraconazole as a risk, and patients experienced ongoing negative outcomes.

The clinical implications of pharmacogenomic variability on itraconazole metabolism have not been thoroughly explored. At this time, there are no Clinical Pharmacogenetics Implementation Consortium guidelines to direct clinician response to pharmacogenomic testing results on itraconazole use and dosing, although drug metabolic pathways suggest a potential influence.[19,20] Itraconazole undergoes hepatic metabolism primarily by CYP3A4, forming more than 30 metabolites, including hydroxy-itraconazole, which has antifungal activity. All metabolites are also inhibitors of CYP3A4, having higher affinity for CYP3A4 than the parent drug.[20] Patient 7's pharmacogenomics indicated reduced CYP3A4 activity, which may have played a role in increased itraconazole exposure and, ultimately, cardiac toxicity.

Limitations

This study has several limitations, chiefly a lack of data on total itraconazole use during the study time frame to determine an exact rate of incidence. One-year sample revealed 316 unique patients issued itraconazole at Mayo Clinic Rochester, suggesting that these toxicities are infrequent. We did not seek to quantify specific patient risk factors or biochemical makers but see these as areas for future exploration. In addition, all the patients in this report were Caucasians, which may limit generalizability of our findings to non-Caucasian patient populations.

CONCLUSION

Over a 20-year span, itraconazole was the probable cause of 31 serious cardiac and fluid disorders at our institution.

Abbreviations and Acronyms: **ADR** = adverse drug event; **CHF** = congestive heart failure; **CV** = cardiovascular; **CYP** = Cytochrome-P; **EF** = ejection fraction; **FDA** = Food and Drug Administration; **HFpEF** = heart failure with preserved ejection fraction; **HFrEF** = heart failure with reduced ejection fraction

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