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.
Clinic Unified Data Platform. Patients without research authorization in Minnesota were excluded. Clinical notes were searched for terms intracva and hypertension, cardiomyopathy, reduced ejection fraction, or edema. Identified patients were reviewed, and the Naranjo adverse drug event (ADE) scoring tool 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 prescription record and provider documentation. 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 (HFrEF 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
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 trans-thoracic 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 1. Patient Characteristics

| Characteristic | Total (N=31) | N (%) |
|----------------|-------------|-------|
| Sex, Male      | 17 (54.8)   |       |
| Age, median (IQR), years | 66 (56, 70) |       |
| Race           | 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.

### Table 2. Summary of CV Toxicity Characteristics

| 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) |       |

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

CV = cardiovascular; CHF = congestive heart failure; EF = ejection fraction.
| ID | Age | Sex | CV comorbidities | ITRA indication | CV toxicity type | Naranjo Score | Time to ADE (weeks) | ITRA oral dose | Formulation | ITRA Load | ITA + H-ITRA level | 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             | 5                 | 200 mg BID capsule | 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   |              | Disseminated histoplasmosis | HTN, edema | 7             | 34                | 200 mg BID capsule | No | 5.9 | Discontinue complete |  |
| 10 | 65  | M   | 1,2          | Disseminated 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 | 4.5 | Discontinue complete |  |
| 13 | 69  | M   | 1,6          | Penosynovitis (NOS) | HFpEF, edema | 7             | 3                 | 200 mg BID capsule | No | 3.1 | Discontinue complete |  |
| 14 | 66  | F   |              | Disseminated Coccidioides | edema | 7             | 1                 | 200 mg BID capsule | Yes | 5.9 | Discontinue complete |  |
| 15 | 50  | M   |              | Pulmonary histoplasmosis | edema, SOB | 7             | 1.5                | 200 mg BID capsule | No | 2.3 | Discontinue no resolution |  |
| 16 | 53  | F   | 3,6          | Disseminated histoplasmosis | HFpEF, edema | 7             | 4                 | Unknown unknown | Unknown | 2.5 | Discontinue complete |  |
| 17 | 63  | M   |              | Prophylaxis | HFpEF, 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 Cryptococcus | HFpEF | 6             | 104               | 200 mg BID capsule | No | 3 | Discontinue 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 | 6.8 | Modify dose no resolution |  |
| 24 | 69  | M   | 5            | Pulmonary (NOS) | HTN | 6             | unknown           | Unknown unknown | Unknown | 6.8 | Modify dose no resolution |  |
| 25 | 63  | M   |              | Disseminated Blastomyces | edema, nocturia | 6             | 67                | 200 mg BID liquid | No | 3.5 | Modify dose partial |  |
| 26 | 66  | F   |              | Pulmonary histoplasmosis | HFpEF | 6             | 4                 | 200 mg QD liquid | No | 2.9 | Modify dose 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 | 2.3 | Discontinue no resolution |  |
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
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. 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. 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. 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. 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; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction

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