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Evaluation of Electrocardiogram (ECG) Monitoring Practice in Newly Initiated Azole Antifungal Therapy

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Abstract

Background: Azole antifungals are first-line options in the management of many fungal infections, but most are known to cause corrected Q-T interval (QTc) prolongation. There is a lack of guidance on which patients warrant ECG monitoring while on azole therapy. We aimed to determine factors associated with ECG monitoring of patients on systemic azole therapy in a real-world setting.

Methods: We performed a retrospective cohort study of hospitalized adult patients who were newly initiated on and received at least 5 days of inpatient azole therapy. Pregnant patients, those on isavuconazole or any azole prior to admission, and those with a gap in azole therapy > 3 days were excluded. Only the first admission with azole use per patient over the study period was included. The primary outcome was whether there was an ECG within 5 days of starting azole therapy. We calculated adjusted odds ratios (aOR) for the association between patient and treatment characteristics and likelihood of ECG measurement using multivariable logistic regression. We also describe factors associated with risk of QTc prolongation in those who had more than one ECG.

Results: 4,126 patients met inclusion criteria over 9 years. Most were admitted to the Hematology/Oncology service (49%), followed by Solid Organ Transplant (20.4%). Azole therapy was initiated for medical prophylaxis in 61.7% and for treatment in 27.9%. Fluconazole (FLU) was the most utilized azole (75.2%), followed by voriconazole (VOR) (18%). Overall, 1,454 patients (35.2%) had at least one ECG measured within 5 days of starting azole therapy. On multivariate analysis, likelihood of having an ECG measured was greater among patients (1) receiving posaconazole (POS, aOR 1.75, 95% CI 1.31-2.34) or VOR (aOR 1.34, 95% CI 1.10-1.63) versus FLU, (2) with a baseline ECG before azole initiation (aOR 2.07 (1.76-2.43), and (3) who received concomitant QT-prolonging medications (aOR 1.22, 95% CI 1.01-1.48) or diuretics (aOR 1.38 95% CI 1.16-1.63).

Conclusion: Use of POS or VOR, baseline ECG monitoring, concomitant QT-prolonging medications, and electrolyte abnormalities, were associated with greater likelihood of ECG monitoring. Further work to understand which patient populations would benefit from ECG monitoring will be imperative.

Background

- **Azole antifungal agents** (except isavuconazole) are known to cause corrected **QTc prolongation**
- No **standardized guidance** exists on which patient warrant ECG monitoring

Objective

- **Evaluate ECG monitoring practices** for initial azole antifungal use at an academic medical center
- Describe **factors associated with QTc prolongation**

Methods

- **Retrospective cohort study** of **hospitalized adults** who received **≥ 5 days of inpatient azole therapy** from 2012-2021; **first admission with azole** use per patient over the study period was included
- Primary outcome: performance of **≥ 1 ECG within 5 days** of azole therapy initiation
- Secondary outcomes: among those with an ECG obtained, assess **frequency of ECG monitoring** and development of **QTc prolongation**
- **We explored associations between patient demographics and treatment characteristics** using univariate and **multivariate regression models**, reported as adjusted odds ratios (aOR).

Results

- 4,126 patients met inclusion criteria. Table 1 summarizes patient characteristics and outcomes. Fluconazole was used in **75.2% of study episodes.** Azoles were most commonly used for **medical prophylaxis (61.7%);** most patients **(83.4%) received ≥1 concomitant potential QT-prolonging agent.**
- Approximately **one-third (1455/4126, 35.3%)** of patients had an **ECG measured within 5 days of initiating an azole;** 397 of these patients (27.3%) had their first ECG obtained within 24 hours of azole initiation and 741 (50.9%) within 48 hours

Table 1. Patient Characteristics and Association with Primary and Secondary Outcomes

Characteristic	Primary Outcome: Measurement of ECG within 5 days of azole start					Secondary Outcome: Presence of QTc prolongation in ≥ 1 ECG after azole initiation among patients meeting primary outcome				
	Characteristic Occurrence by Population: mean (SD) or n (%)			Odds Ratio for ECG within 5 days of azole start		Characteristic Occurrence by Population: mean (SD) or n (%)			Odds Ratio for QTc prolongation[T] after azole start	
	Total population (N=4126)	No ECG within 5 days of azole start (n=2671)	ECG within 5 days of azole start (n=1455)	Unadjusted Odds Ratio (95% CI)	Adjusted* Odds Ratio (95% CI)	Total population (N=1455)	No prolonged QTc after azole initiation (n=1249)	≥ 1 ECGs with prolonged QTc after azole initiation (n=206)	Unadjusted Odds Ratio (95% CI)	Adjusted* Odds Ratio (95% CI)
Gender (female)	1812 (43.9%)	1185 (44.4%)	627 (43.1%)	0.95 (0.83-1.08)	0.95 (0.82-1.09)	627 (43.1%)	546 (43.7%)	81 (39.3%)	0.83 (0.62-1.12)	0.89 (0.65-1.25)
Age (years)	55.4 (15.3)	55.3 (15.3)	55.7 (15.2)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	55.6 (15.2)	55.5 (15.4)	56.5 (14.1)	1.00 (0.99-1.01)	1.00 (0.99-1.01)
LOS after starting azole (days)	15.2 (13.4)	14.4 (12.8)	16.7 (14.2)	**1.01 (1.01-1.01)**	1.00 (0.99-1.01)	16.7 (14.2)	15.7 (12.8)	22.5 (20.0)	**1.03 (1.02 - 1.03)**	1.00 (0.99-1.01)
ECG pre-azole	2603 (63.1%)	1463 (54.8%)	1140 (78.4%)	**2.98 (2.58-3.45)**	**2.08 (1.78-2.45)**	1140 (78.3%)	958 (76.7%)	182 (88.4%)	**2.30 (1.47-3.59)**	1.23 (0.76-2.02)
ID Consult	363 (8.8%)	222 (8.3%)	141 (9.7%)	1.18 (0.95-1.48)	0.96 (0.75-1.22)			Not analyzed		
Service										
Medicine	595 (14.4%)	375 (14.0%)	220 (15.1%)	**Reference**	**Reference**			Not analyzed		
Oncology	2022 (49.0%)	1467 (54.9%)	555 (38.1%)	**0.64 (0.53-0.78)**	0.81 (0.62-1.07)			Not analyzed		
Surgery	542 (13.1%)	358 (13.4%)	184 (12.7%)	0.88 (0.69-1.12)	0.95 (0.73-1.25)			Not analyzed		
Solid Organ Transplant	841 (20.4%)	388 (14.5%)	453 (31.1%)	1.99 (1.61-2.47)	1.33 (0.98-1.81)			Not analyzed		
Other	126 (3.1%)	83 (3.1%)	43 (3.0%)	0.88 (0.59-1.32)	0.89 (0.58-1.38)			Not analyzed		
Azole										
Fluconazole	3102 (75.2%)	2136 (80.0%)	966 (66.4%)	**Reference**	**Reference**	966 (66.4%)	821 (65.7%)	145 (70.4%)	**Reference**	**Reference**
Itraconazole	16 (0.4%)	9 (0.3%)	7 (0.5%)	1.72 (0.64-4.63)	1.71 (0.59-4.97)	7 (0.5%)	7 (0.6%)	0 (0.0%)	N/A	N/A
Posaconazole	266 (6.5%)	141 (5.3%)	125 (8.6%)	**1.96 (1.52-2.52)**	**1.72 (1.30-2.28)**	125 (8.6%)	115 (9.2%)	10 (4.9%)	**0.49 (0.25-0.96)**	0.83 (0.39-1.74)
Voriconazole	742 (18.0%)	385 (14.4%)	357 (24.5%)	**2.05 (1.74-2.41)**	**1.33 (1.09-1.62)**	357 (24.5%)	306 (24.5%)	51 (24.8%)	0.94 (0.67-1.33)	0.75 (0.49-1.15)
Azole Indication										
Medical Prophylaxis	2546 (61.7%)	1707 (63.9%)	839 (57.7%)	**Reference**	**Reference**	839 (57.6%)	740 (59.3%)	99 (48.1%)	**Reference**	**Reference**
Treatment	1151 (27.9%)	704 (26.4%)	447 (30.7%)	**1.29 (1.12-1.49)**	1.08 (0.87-1.35)	447 (30.7%)	362 (28.9%)	85 (41.3%)	**1.76 (1.28-2.41)**	1.27 (0.88-1.84)
Other	429 (10.4%)	260 (9.7%)	169 (11.6%)	**1.32 (1.07-1.63)**	0.96 (0.74-1.26)	169 (11.6%)	147 (11.8%)	22 (10.7%)	1.11 (0.68-1.83)	1.01 (0.57-1.79)
Past Medical History										
Transplant Recipient (SOT or stem cell)	636 (15.4%)	305 (11.4%)	331 (22.8%)	**2.28 (1.93-2.71)**	1.03 (0.80-1.33)	331 (22.8%)	253 (20.3%)	78 (37.9%)	**2.39 (1.75-3.28)**	1.40 (0.96-2.04)
Dialysis	357 (8.7)	196 (7.3)	161 (11.1)	**1.57 (1.26-1.96)**	1.13 (0.89-1.44)	161 (11.1%)	119 (9.5%)	42 (20.4%)	**2.43 (1.64-3.58)**	1.36 (0.89-2.10)
Active Smoker	410 (9.9%)	266 (10%)	144 (9.9%)	0.99 (0.80-1.23)	1.05 (0.83-1.33)	144 (9.9%)	122 (9.8%)	22 (10.7%)	1.10 (0.68-1.78)	1.29 (0.76-2.19)
Thyroid Abnormalities	195 (4.7%)	124 (4.6%)	71 (4.9%)	1.05 (0.78-1.42)	1.08 (0.78-1.50)	71 (4.9%)	60 (4.8%)	11 (5.3%)	1.12 (0.58-2.16)	1.17 (0.56-2.42)
HIV	88 (2.1%)	60 (2.3%)	28 (1.9%)	0.85 (0.54-1.34)	0.81 (0.49-1.33)	28 (1.9%)	25 (2.0%)	3 (1.5%)	0.72 (0.22-2.41)	0.95 (0.26-3.42)
CV Disease	1862 (45.1%)	1131 (42.3%)	731 (50.2%)	**1.37 (1.21-1.56)**	1.13 (0.97-1.31)	731 (50.2%)	589 (47.2%)	142 (68.9%)	**2.48 (1.81-3.41)**	**1.85 (1.29-2.64)**
Bradycardia	2453 (59.5%)	1591 (59.6%)	862 (59.2%)	0.99 (0.87-1.12)	0.97 (0.83-1.12)	862 (59.2%)	726 (58.1%)	136 (66.0%)	**1.39 (1.02-1.91)**	1.24 (0.88-1.75)
Atrial Fibrillation	149 (3.6%)	70 (2.6%)	79 (5.4%)	**2.13 (1.54-2.96)**	**1.76 (1.23-2.51)**	79 (5.4%)	62 (4.9%)	17 (8.3%)	1.72 (0.98-3.01)	1.22 (0.66-2.27)
Hepatic Disease	528 (12.8%)	336 (12.6%)	192 (13.2%)	1.06 (0.87-1.28)	1.11 (0.90-1.37)	192 (13.2%)	172 (13.8%)	20 (9.7%)	0.67 (0.41-1.09)	0.64 (0.38-1.09)
Concomitant Medications During Azole Therapy										
QT-prolonging medications[a]	3440 (83.4%)	2241 (83.9%)	1199 (82.4%)	0.90 (0.76-1.07)	**1.21 (1.00-1.48)**	1199 (82.4%)	1031 (82.6%)	168 (81.6%)	0.93 (0.64-1.37)	1.20 (0.79-1.81)
Diuretics/ Electrolyte Disturbing Agents[b]	1547 (37.5%)	801 (30.0%)	746 (51.3%)	**2.46 (2.15-2.80)**	**1.38 (1.16-1.61)**	746 (51.3%)	592 (47.4%)	154 (74.7%)	**3.28 (2.35-4.58)**	**1.95 (1.31-2.89)**
Abnormal Labs During Azole Therapy										
Calcium (< 8.5 mEq/L)	2371 (57.5%)	1359 (50.9%)	1012 (69.6%)	**2.2 (1.93-2.52)**	**1.24 (1.05-1.47)**	1012 (69.6%)	820 (65.6%)	192 (93.2%)	**7.18 (4.12-12.5)**	**4.01 (2.14-7.52)**
Magnesium (< 1.7 mEq/L)	2181 (52.9%)	1303 (58.8%)	878 (60.3%)	**1.60 (1.40-1.82)**	**1.16 (1.00-1.33)**	878 (60.3%)	747 (59.8%)	131 (63.6%)	1.17 (0.86-1.59)	0.85 (0.59-1.19)
Potassium (> 5 mEq/L)	1468 (35.6%)	815 (30.5%)	653 (44.9%)	**1.85 (1.62-2.12)**	1.10 (0.94-1.29)	653 (44.9%)	519 (41.6%)	134 (65.1%)	2.61 (1.92-3.56)	1.30 (0.91-1.87

CV: cardiovascular, ECG: electrocardiogram, HIV: human immunodeficiency virus ID: infectious diseases, LOS: length of stay
*Concomitant use during azole therapy: Antibiotics (ciprofloxacin, levofloxacin, moxifloxacin, clarithromycin, azithromycin), HIV (protease inhibitors), CV meds (amiodarone, disopyramide, dofetilide, procainamide, quinidine, sotalol), antiemetics (chlorpromazine, metoclopramide, ondansetron), chemotherapy (nilotinib, sunitinib), antipsychotics (haloperidol, risperidone, ziprasidone), miscellaneous (methadone) [F]Furosemide, bumetanide, torsemide, sulfamethoxazole-trimethoprim, amphotericin use during azole therapy
*Adjusted Odds Ratio: all characteristics analyzed Table 1 were included in the corresponding multivariable models for the outcome of interest
[T]Prolonged QTc: Narrow complex QRS: > 500 msec; Wide-complex QRS (> 120 msec): > 550 msec

Results (cont'd)

- Among patients with ECGs on antifungals, **median number of ECGs** obtained **during the duration of inpatient azole use was 2** (interquartile range 1-4, range 1-122).
- On multivariable analysis (Table 1), statistically significant **predictors of ECG monitoring within 5 days of azole initiation** were measurement of a **prior ECG**, **use of posaconazole or voriconazole (versus fluconazole)**, medical history **of atrial fibrillation**, receipt of **concomitant QT-prolonging or electrolyte-altering agents**, and an **abnormal calcium or magnesium level**
- Among patients with ECG monitoring, **14.1% (206/1455)** had at **least one ECG that met criteria for QTc prolongation**. In the subset of patients with a pre-azole ECG and ECG monitoring, **139/1140 (12.2%) had a QTc prolongation of >60 msec** from pre-azole values.
- Across azoles, a prolonged QTc was measured at least once in **15.0% of fluconazole courses (145/966), 0% of itraconazole courses (0/7), 8.0% of posaconazole courses (10/125), and 14.3% of voriconazole courses (51/357).** In multivariable analysis (Table 1), **CV disease, use of diuretics/electrolyte disturbing agents, and hypercalcemia** were associated with **QTc prolongation** during azole use

Conclusions

- One-third of patients initiating azole antifungal therapy had an ECG performed within 5 days of starting therapy. **Clearer criteria for performing ECG monitoring** in patients on azoles should be considered.
- Patients receiving posaconazole and voriconazole were more likely to have an ECG measured relative to fluconazole, although among patients with ECG measurement they were no more likely to have QTc prolongation. **The QTc prolongation risk of fluconazole may be underestimated by clinicians**.
- More studies and **guidance on best practices are needed** to guide use of ECGs during azole therapy

Limitations

- **Single-center study** with **retrospective** data collection
- Limited ability to identify QTc prolongation risk factors, potential for **unmeasured confounding**
- No well-determined **standard for appropriateness of ECG monitoring** in patients on azoles
- Lack of clinical outcome data (i.e. Torsades de Pointes, mortality)