Torsade de Pointes/QT Prolongation Associated with Antifungal Triazoles: A Pharmacovigilance Study Based on the U.S. FDA Adverse Event Reporting System（FAERS）

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ABSTRACT -- Purpose: Torsade de pointes (TdP)/QT prolongation is a fatal adverse event (AE) when using antifungal triazoles. We aimed to compare the AE signals of TdP/QT prolongation and onset time among different drugs of this kind comprehensively. **Methods:** This retrospective research was to analyze the U.S. FDA Adverse Event Reporting System (FAERS) database containing 71 quarters of reports through online retrieval. We calculated the strength of signals of TdP/QT prolongation related to 4 drugs of triazoles by using the following indicators: reporting odds ratio (ROR), proportional reporting ratio (PRR), information component (IC), and empirical Bayesian geometric mean (EBGM). The onset time to the AE of TdP/QT prolongation among different antifungal triazoles were compared by using nonparametric tests. Management and visualization of the data were performed by employing MySQL Workbench and R software. The data information including clinical features, AE onset time, and outcomes were extracted for analysis as well. **Results:** After filtering the FAERS database, 448 reports were identified that were associated with TdP/QT prolongation when 4 triazoles played the primary suspected role. The AE signals of TdP/QT prolongation for any involved antifungal triazoles were detected by using the 4 detection indicators, and the signals of fluconazole are the strongest. This AE mostly occurred within 0-14 days after triazoles therapy. **Conclusions:** The AE signals of TdP/QT prolongation associated with antifungal triazoles were very intense. Attention must be paid to the TdP/QT prolongation of various triazoles, particularly at the early stages of antifungal triazoles treatment.

INTRODUCTION

The morbidity of fungal infections is continually rising, particularly in immunocompromised patients (1). Specifically, systemic fungal infections could cause serious consequences to patients with poor prognosis. Triazoles act as antifungal agents by affecting the synthesis of ergosterol, which is typical of fungal cell membranes (2, 3). However, triazoles do not only target fungal-associated enzymes, but also interfere with mammalian enzymes, which can cause adverse off-target effects (4). Triazoles are a popularly used kind of antifungal agents in clinical practice, which mainly includes fluconazole, itraconazole, posaconazole and voriconazole (2, 5, 6). Furthermore, antifungal infection prophylaxis can be performed with itraconazole, posaconazole and voriconazole (7, 8). Pharmacokinetic properties are different for various agents of triazoles and vary widely among individuals (9). Although the efficacy of triazoles has been proven, the risk of toxicity associated with long-term use of them has raised concerns.

Cardiovascular adverse events associated with triazoles have attracted increasing awareness. In recent years, a growing number of torsade de pointes (TdP)/QT prolongation related to triazoles have been reported (10). QT prolongation is an etiological factor of TdP that is a life-threatening dysrhythmia disease related to the risk of sudden cardiac death (11, 12). Therefore, the characteristics of the occurrence of TdP/QT prolongation associated with triazoles deserve to be explored deeply for safe use of these drugs.

Data mining is a useful method for signal detection in pharmacovigilance recommended by the report of the Council for International Organizations of Medical Sciences (CIOMS) working group (13). Data mining can be valuable not only for monitoring the safety of new drugs but also for the continuous

supervising of older drugs. Few studies have been conducted to mine triazoles-associated AE signals by combining algorithms with real-world data.

The AE Reporting System created by the US FDA (FDA AERS or FAERS) is an enormous database of adverse event (AE) reports covering drugs, biologics, and certain other medicinal products through a spontaneous reporting system (SRS) (14). Besides, all reports in the FAERS database are available on the official website of the FDA completely and freely (15).

METHODS

Data source

The FDA public website provides the data of AE records from quarter 1 of 2004 (2004Q1) to quarter 3 of 2021 (2021Q3), and we fetched back full data from the website (15). The website has two available data formats, ASCII, and XML, and we have picked the former for data mining. All data for AE reports is preserved in seven subfiles separately, including DEMOyyQq (provides patient's baseline information), DRUGyyQq (contains drug information), REACyyQq (recodes adverse events), OUTCyyQq (includes patient outcomes), RPSRyyQq (provides report sources), THERyyQq (recodes therapy data), and INDIyyQq (recodes indication for drugs). The "primaryid" is the unique value used to identify the reports, it is the primary key that could be used to link and query the information among all subfiles.

Discrimination of objective drugs and AE

Fluconazole, itraconazole, posaconazole and voriconazole were enrolled in our investigation. Given that FAERS does not use a uniform coding system for the medications, brand names, generic names, abbreviations, and designation names were utilized to distinguish records related to triazoles in the DRUGyyQq files. The Standardized MedDRA (Medical Dictionary for Regulatory Activities, MedDRA® trademark is registered by ICH, version 24.0) queries (SMQs) are validated, standard sets of MedDRA terms, TdP/QT prolongation SMQ were used to identify the goal AE (16).

Statistical analysis

FDA recommends that the following rules be followed when cleaning up data in DEMOyyQq files: when two items have the equivalent "caseids", the most current "fda_dt" would be elected; furthermore, we picked the higher "primaryid" while the "caseid" and the "fda_dt" are sameness.

We collected and extracted the data, including baseline information, outcomes, and onset time of patients with TdP/QT prolongation AE associated with the involved triazoles after data cleaning and screening. Disproportionality analysis (DPA) is one of the popular signal detection algorithms, which mainly contains 4 detection indicators, including the reporting odds ratio (ROR), proportional reporting ratio (PRR), information component (IC), and empirical Bayesian geometric mean (EBGM). ROR and PRR are based on ROR and PRR algorithm respectively. Both are convenient to calculate, and the results are easy to understand but tend to have false-positive results for a small number of cases (17). The IC is calculated by the Bayesian Confidence Propagation Neural Network (BCPNN) algorithm, which gives valid results even in the presence of missing data, but it is computationally complex and relatively insensitive (18). The evaluation index of the Multi-item Gamma Poisson Shrinker (MGPS) algorithm is EBGM, in which variables are included hierarchically and the influence of confounding factors can be reduced. It can effectively avoid false positives, but its calculation process is relatively complicated (17). The formulae for the four methods are presented in Table SUPPL 1 and Table SUPPL 2. The THERyyQq files and DEMOyyQq files were combined by “primaryid” that was used to calculate the occurrence time by “event_dt” and “start_dt”, after removing irrational data. Management and visualization of the data were performed by employing the MySQL Workbench software, version 8.0.21 (Oracle Corporation, Austin, Texas, US) and the R software, version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria.).

The onset TdP/QT events prolongation time occurrence following triazoles treatment measured as interquartile range (IQR) among different antifungal triazoles was compared by using nonparametric tests (the Mann-Whitney test for dichotomous variables and the Kruskal-Wallis test when there were more than two groups). Statistical significance was recognized as a two-sided P value of less than 0.05 (19).

RESULTS

The DEMOyyQq files in the FAERS database involved 16842059 records from 2004Q1 to 2021Q3, and we retrieved 14130306 reports followed by FDA

recommendations. 20250 cases were regarded as TdP/QT prolongation, of which 448 cases were reported after the involved triazoles treatment (Figure 1).

The clinical baseline data of cases with triazoles induced TdP/QT prolongation was described in Table 1. The highest percentage of records of TdP/QT prolongation was found to be related to fluconazole (61.61%). More cases of triazoles-related TdP/QT prolongation were found in the patient group of 45~65 years old (31.7%). The share of the female and male is nearly in total (27.46% vs. 26.56%). The largest number of records were reported by physician (40.18%), and the second was reported by the pharmacist (16.74%).

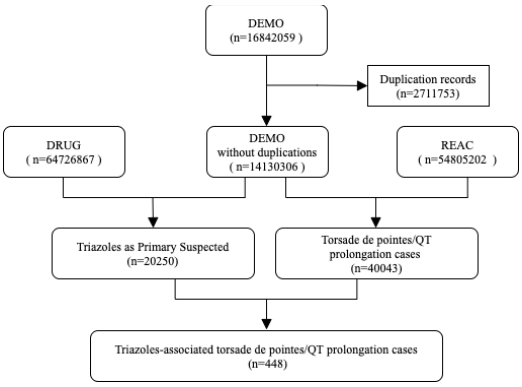

Figure 1. The selection process of TdP/QT prolongation cases linked to triazoles from FAERS database.

The results of data-mining algorithms were summarized in Table 2. Overall, the values of all four methods indicated that the therapeutic use of triazoles was correlated with TdP/QT prolongation. In terms of the criteria of signal detection, fluconazole demonstrated the strongest potential correlation to TdP/QT prolongation, with the values of ROR (13.12, 95% CI 2.69 to 14.80), PRR (12.68, $\chi 2$ 2958.63), IC (3.66, 95% CI 3.24 to 4.12) and EBGM (12.60, EBGM05 11.17).

We described the onset time for each antifungal triazole in Figure 2. It is noteworthy that TdP/QT prolongation adverse effects could occur within 0-14 days after taking all the four triazoles. The onset time of the Torsade de pointes/QT prolongation associated with voriconazole, fluconazole, itraconazole and posaconazole ranges were 0-31, 0-697, 3-581 and 0-657 days, respectively. The median onset time of TdP/QT prolongation among different agents of antifungal triazoles was 9 (IQR 2-11) days for voriconazole, 10 (IQR 2-85) days for fluconazole8 (IQR 3-30) days for itraconazole and 15 (IQR 10-24) days for posaconazole. There was no statistically significant difference in onset time to the AE of TdP/QT prolongation among the four antifungal triazoles (Kruskal-Wallis test, P = 0.093).

The outcomes of TdP/QT prolongation AE induced by triazoles therapy were summarized in Table 3, mainly involving serious outcomes. In total, triazoles-related to TdP/QT prolongation resulted in 218 (29.30%) cases of hospitalization-initial or prolonged.

DISCUSSION

The main objective of this retrospective pharmacovigilance investigation is to compare the signals and onset time of TdP/QT prolongation AE among various triazoles, based on the real-world data records involved 71 quarters of the FAERS. Four data-mining indicators were employed to detect the TdP/QT prolongation signals. Furthermore, we summarized the clinical features, time of occurrence, and prognosis of the patients enrolled. In general, the results showed that the strength of signals of TdP/QT prolongation associated with triazoles was intense, according to the four assays of ROR, PRR, IC, and EBGM.

Prospective observational research found voriconazole-related cardiac tachyarrhythmias AE (20). Teaford H.R. et al reported a case that suffered QT prolongation after using itraconazole for five weeks (21). A study determined a 16.2% incidence of QT prolongation and an absolute risk of 2.7% for TdP (12). Pasternak, Y. et al indicated a high prevalence of clinically significant QT prolongation in children treated with voriconazole (22). Triazoles causing TdP/QT prolongation had been reported in clinical practices, however, the precise pharmacovigilance signal strength of it still doesn't be reported. A study found that patients treated with itraconazole had fewer composite safety outcomes compared to patients who used voriconazole or posaconazole due to a lower incidence of QT prolongation (23). Consequently, it is notable to concern this AE by using real-world clinical data. Data mining for AE signals in pharmacovigilance investigation has become increasingly prevalent in recent years. Our data further confirmed the TdP/QT prolongation pharmacovigilance signals related to the triazoles therapy with four indicators, ROR,

Table 1. The clinical information of cases with the AE of TdP/QT prolongation related to triazoles.

Baseline information	Number of reports (%)				
	Fluconazole	Itraconazole	Posaconazole	Voriconazole	Total
Total	276 (61.61)	59 (13.17)	45 (10.04)	68 (15.18)	448 (100)
Age group					
<18 years	12 (4.35)	0 (0)	4 (8.89)	15 (22.06)	31 (6.92)
18–44 years	59 (21.38)	8 (13.56)	6 (13.33)	3 (4.41)	76 (16.96)
45-64 years	98 (35.51)	13 (22.03)	18 (40)	13 (19.12)	142 (31.7)
≥ 65 years	80 (28.99)	18 (30.51)	8 (17.78)	22 (32.35)	128 (28.57)
Abnormal or missing	27 (9.78)	20 (33.9)	9 (20)	15 (22.06)	71 (15.85)
Sex					
Female	72 (26.09)	15 (25.42)	16 (35.56)	20 (29.41)	123 (27.46)
Male	72 (26.09)	9 (15.25)	12 (26.67)	26 (38.24)	119 (26.56)
Abnormal or missing	132 (47.83)	35 (59.32)	17 (37.78)	22 (32.35)	206 (45.98)
Reporter					
Physician	119 (43.12)	20 (33.9)	19 (42.22)	22 (32.35)	180 (40.18)
Pharmacist	38 (13.77)	19 (32.2)	6 (13.33)	12 (17.65)	75 (16.74)
Consumer	9 (3.26)	3 (5.08)	7 (15.56)	5 (7.35)	24 (5.36)
Others or missing	110 (39.86)	17 (28.81)	13 (28.89)	29 (42.65)	167 (37.72)
Year					
2021	6 (2.17)	8 (13.56)	4 (8.89)	12 (17.65)	30 (6.7)
2020	33 (11.96)	8 (13.56)	7 (15.56)	11 (16.18)	59 (13.17)
2019	19 (6.88)	4 (6.78)	2 (4.44)	6 (8.82)	31 (6.92)
2018	24 (8.7)	2 (3.39)	10 (22.22)	6 (8.82)	42 (9.38)
2017	27 (9.78)	6 (10.17)	7 (15.56)	13 (19.12)	53 (11.83)
2016	23 (8.33)	2 (3.39)	3 (6.67)	4 (5.88)	32 (7.14)
2004-2015	139 (50.36)	29 (49.15)	12 (26.67)	15 (22.06)	195 (43.53)
Abnormal or missing	5 (1.81)	0 (0)	0 (0)	1 (1.47)	6 (1.34)

Table 2. The AE signals of TdP/QT prolongation associated with triazoles.

Drugs	N	ROR (95% CI)	PRR (χ^2)	IC (95% CI)	EBGM ($EBGM_{05}$)
Total	448	8.04 (2.18, 8.83) *	7.88 (2669.72) *	2.96 (2.7, 3.26) *	7.81 (7.10) *
Fluconazole	276	13.12 (2.69, 14.80) *	12.68 (2958.63) *	3.66 (3.24, 4.12) *	12.60 (11.17) *
Itraconazole	59	6.55 (2.14, 8.48) *	6.45 (272) *	2.69 (2.08, 3.48) *	6.44 (4.98) *
Posaconazole	45	6.64 (2.19, 8.91) *	6.53 (211.19) *	2.71 (2.01, 3.63) *	6.53 (4.86) *
Voriconazole	68	3.53 (1.50, 4.48) *	3.50 (121.7) *	1.81 (1.42, 2.29) *	3.50 (2.75) *

N, the number of adverse event reports; PRR, the proportional reporting ratio; χ2, chi-squared; ROR, the reporting odds ratio; IC, the information component; EBGM, the empirical Bayes geometric mean; CI, confidence interval; two-sided for ROR and IC, and one-sided for EBGM.
* Signal was considered significant, see Table SUPPL 2 for evaluation details.

Table 3. The percent of outcomes of each triazole-induced to TdP/QT prolongation.

Outcomes	Number of outcomes (%)				
	Fluconazole	Itraconazole	Posaconazole	Voriconazole	Total
Death	23 (4.94)	6 (6.82)	9 (11.39)	12 (10.81)	50 (6.72)
Life-threatening, n (%)	99 (21.24)	15 (17.05)	14 (17.72)	26 (23.42)	154 (20.70)
Hospitalization-initial or prolonged, n (%)	140 (30.04)	26 (29.55)	19 (24.05)	33 (29.73)	218 (29.30)
Disability, n (%)	2 (0.43)	0 (0)	2 (2.53)	0 (0)	4 (0.54)
Others, n (%)	202 (43.35)	41 (46.59)	35 (44.30)	40 (36.04)	318 (42.74)
Total, n (%)	466 (100.00)	88 (100.00)	79 (100.00)	111 (100.00)	744 (100.00)

Multiple outcomes may be recorded for the same one case.

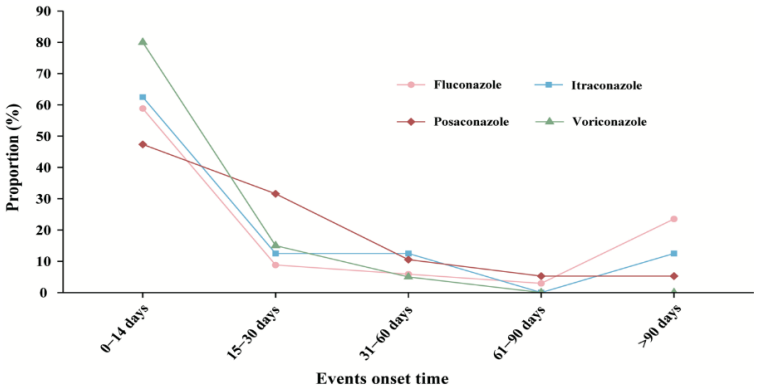

Figure 2. The proportion of the onset time of TdP/QT prolongation events occurrence following triazoles treatment.

PRR, IC05 and EBGM05.

TdP/QT prolongation might lead to serious and even fatal outcomes and proactive prevention and management of it is highly warranted. A possible mechanism of drug-induced QT prolongation is blocking repolarizing potassium currents by inhibiting potassium efflux channels (24). Two studies found that hypokalemia was significantly related to QT prolongation (12, 20). It is of great value to perform monitoring of ECG and serum electrolyte concentrations. At the same time, therapeutic drug monitoring (TDM) is beneficial for effective, rational, and safe use of triazoles (25). Itraconazole, voriconazole and posaconazole require TDM, on the other hand, there is no publicly available data for isavuconazole (26).

To our knowledge, only a few studies have reported the onset time of TdP/QT prolongation adverse events caused by antifungal triazoles. Research showed that the median latency times of TdP/QT prolongation adverse events after starting antifungal triazoles therapy ranged from 1 day (posaconazole) to 9.5 days (itraconazole) (10). We further calculated the median onset time of antifungal triazoles-associated TdP/QT prolongation and compared their difference. There were no statistically significant differences between the examined drugs possibly due to the wide range of observations (P = 0.093). Although the significant difference wasn't identified, we found that TdP/QT prolongation adverse effects could occur within seven days after taking all four triazoles. It reminds us that we should pay special attention to the TdP/QT prolongation of various triazoles, particularly at the early stages of antifungal triazoles treatment.

The FAERS database provides extensive, freely accessible information on real-world clinical data, but inevitably, there still existed the limitations in our investigation. Firstly, since it is based on the SRS, a great deal of data may be missing or unknown, and due to the objective situation, that the drug names were not standardized, they may be omitted in the query process. Secondly, it is hard to calculate the exact incidence given that the number of patients who use triazoles was not available. And many potential confounders existed preventing us from further exploring the possible association between AE and clinical features due to the absence of interventions. Thirdly, concomitant drugs have not been considered, we will perform relevant drug interaction research in the future. Finally, several new data mining algorithms are being developed and applied, we have only used one of them. We plan to apply more algorithms to pharmacovigilance research. Despite these drawbacks, the sample size of the database is enormous. The prevalence and risk of TdP/QT prolongation caused by triazoles need to be further explored in prospective RCT studies.

CONCLUSION

Triazoles are increasingly used in clinical practice for antifungal triazoles therapy. Our present study confirms the antifungal triazoles-associated TdP/QT prolongation that occurs 0-14 days after the therapy commencement.

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AUTHOR CONTRIBUTIONS. ZC Yu and XL Liao designed the study, and XL Liao mainly performed the part of data analysis, all authors contributed to writing this paper.

CONFLICT OF INTEREST. The authors declare that they have no conflicts of interest.

SOURCE OF FUNDING. None.

DATA AVAILABILITY. The data used to support the findings of this study are available from the corresponding or first author upon request.

ETHICS. Not applicable.

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