Hepatic dysfunction events associated with voriconazole: a real-world study from FDA adverse event reporting system (FAERS) database

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Abstract

Aims: Although voriconazole-induced hepatotoxicity has been reported previously, the direct cause-effect relationship in the real world remains to be established. The aim of this study was to investigate the association between voriconazole and hepatic dysfunction based on the FAERS database. Methods: Data from January 2004 to March 2022 in FAERS were retrieved. We estimate the association between the hepatic dysfunction and voriconazole using reporting odds ratios (RORs) for mining the adverse event report signals and compare voriconazole with the full database and other antifungal drugs. Results: 646 reports of hepatic dysfunction related to voriconazole as the primary suspect drug were collected totally. The median time to event of the hepatic dysfunction events was 8 (interquartile range [IQR] 2-28) days. 62.20% hepatic-related adverse events appeared within the first 15 days since the initiation of voriconazole administration. The overall ROR (95% CI) for hepatic-related adverse events was 6.82 (95% CI 6.26-7.42). Comparing to other antifungal drugs, the RORs for hepatic-related adverse events of fluconazole, isavuconazole and amphotericin B were 2.19 (95% CI 1.94-2.47), 2.31 (95% CI 1.66-3.33) and 1.26 (95% CI 1.08-1.48), respectively. Conclusions: We observed strong signals of higher frequency of reporting hepatic dysfunction events associated with voriconazole in the events of hepatic dysfunction. Since the risk of developing liver injury and possible hepatic dysfunction by voriconazole depends on several factors including underlying hepatic disease, close clinical and laboratory monitoring, including therapeutic drug monitoring (TDM), are essential to prevent or promptly recognize further deterioration of the hepatic function.

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Conclusions : We observed strong signals of higher frequency of reporting hepatic dysfunction events associated with voriconazole in the events of hepatic dysfunction. Since the risk of developing liver injury and possible hepatic dysfunction by voriconazole depends on several factors including underlying hepatic disease, close clinical and laboratory monitoring, including therapeutic drug monitoring (TDM), are essential to prevent or promptly recognize further deterioration of the hepatic function.

Keywords : voriconazole, hepatic dysfunction, invasive aspergillosis, real-world study, FAERS

INTRODUCTION

Invasive aspergillosis is a life-threatening infection among individuals with long-lasting or severe impairment of the immune system [1]. Compared with other triazole antifungals, voriconazole has enhanced activity against the Aspergillus species, and as an alternative therapy for candidemia, in individuals who do not have neutropenia [2, 3], so it remains the standard of care and is recommended by international guidelines for the primary treatment of invasive aspergillosis [4, 5]. Although voriconazole-induced hepatotoxicity has been reported previously, the direct cause-effect relationship remains to be established systematically based on the real world data.

The FAERS includes several million spontaneous reports of drug-associated adverse events and is used to evaluate drug safety profiles. The database includes all adverse drug events (ADEs) information and medication error information collected by the FDA. It is one of the primary tools used for post-marketing surveillance and pharmacovigilance [6]. We conducted this study to examine the association between voriconazole and hepatic dysfunction, and compared RORs of hepatic dysfunction caused by voriconazole and other antifungal drugs. All data analysis is based on FAERS database.

2. METHODS

In this study, we followed the method of Mingxing Guo et al. and the methods description partly reproduced their wording [7].

2.1 Data Source

This study was designed as a retrospective study, the interventions of interest was voriconazole. All records in the FAERS database from January 2004 to March 2022 were included in this study [8]. We used both generic names and brand names to identify voriconazole and control drugs (see details in **Supplementary Materials Table S1**).

A deduplication procedure was performed according to the FDA's recommendations to select the latest FDA_DT with the same CASEID and select the higher PRIMARYID when CASEID and FDA_DT are both the same adverse events (AE) were included when they were considered the "Primary Suspect (PS) drug (drugs which directly suspected of causing the adverse events)".

2.2 Definition of hepatic dysfunction Events

We identified hepatic dysfunction events which were in preferred terms (PTs) using Medical Dictionary for Regulatory Activities terms (V23.0). Different PTs were identified with the Standardized MedDRA Query (SMQ) for "livery injury", "liver related", "hepatic failure" and "acute hepatic failure" and the System

Organ Class (SOC) for hepatobiliary disorder, and only reports that met both criteria were extracted. One case could be reported more than one PTs of the same SMQ, duplicate records was removed, the number of selected PTs was 48 (see details in **Supplementary Materials Table S2**).

2.3 Analysis

We performed disproportionality analysis using the reporting odds ratio (ROR) with relevant Confidential Interval (CI) to indicate the presence of signals of potential increased risk of drug-related AE [9]. The ROR was calculated by dividing the odds of hepatic dysfunction events reporting for voriconazole by the odds of hepatic dysfunction events reporting for the comparison drug. A signal of increased hepatic dysfunction risk was defined as the lower limit of 95% CI exceed one with the number of cases [?]3 [10].

To validate the robustness of the findings, we conducted five specific comparisons: (1) compared voriconazole with the full database; (2) compared voriconazole with the other triazole antifungal drugs: fluconazole, itraconazole, posaconazole and isavuconazole; (3) compared voriconazole with the echinocandins antifungal drugs: caspofungin, micafungin and anidulafungin; (4) compared voriconazole with the polyene antifungal drug amphotericin B; (5) compared voriconazole with the 5-fluorocytosine.

The primary outcomes were overall hepatic-related adverse events compared with the full database and the other antifungal drugs (see details in **Supplementary Materials Table S3**). The secondary outcomes were the high frequency reporting of hepatic dysfunction events (see details in **Supplementary Materials Table S4/S5**): hepatic function abnormal, cholestasis, alanine aminotransferase increased, blood alkaline phosphatase increased, aspartate aminotransferase increased, liver function test abnormal, gamma-glutamyl transferase increased, liver disorder, hepatocellular injury, blood bilirubin increased.

All the data extraction were performed by Microsoft Access 2010, and the statistical analyses were performed using SPSS 26.0.

3. RESULTS

3.1 Descriptive analysis

After data cleaning, 17,710,899 reports in the FAERS database were of use. Overall, from January 2004 to March 2022, there were 3694 reports listing voriconazole were identified as PS, the number of hepatic dysfunction events was 646 (17.48%). The clinical characteristics of patients with voriconazole induced hepatic dysfunction were described in**Table 1** . The hepatic disorders associated with voriconazole were slightly higher in male than in female (56.50% vs. 33.90%, P¡0.05), and 27.40% of them are elderly patients ([?]65 years old). The fatality rate of the reported hepatic disorders was 9.75%, which is lower than non-hepatic disorders.

The median time to event of the hepatic dysfunction events was 8 (IQR 2-28) days, and 62.20% of patients developed hepatic dysfunction in 15 days of voriconazole use (**Fig. 1**).

Table 1 The clinical characteristics of patients

		Hepatic disorder events (%)	Non-hepatic disorders events (%)
Gender	Gender	Gender	Gender
	F	219(33.90)	1304(35.30)
	M	365(56.50)	2273(61.53)
	Miss/Unknown	62(9.60)	117(3.17)
Age	Age	Age	Age
	[?]65y	177(27.40)	1059(28.67)
	¡65y	396(61.30)	2390(64.70)
	Miss/Unknown	73(11.30)	245(6.63)
Outcome*	Outcome*	Outcome*	Outcome*
	DE	63(9.75)	931(25.20)

		Hepatic disorder events (%)	Non-hepatic disorders events (%)
	DS	8(1.24)	49(1.33)
	HO	146(22.60)	762(20.63)
	LT	20(3.10)	102(2.76)
	OT	370(57.28)	1691(45.78)
	RI	3(0.46)	5(0.14)
	MISS	36(5.57)	154(4.17)
OCCP#	OCCP#	OCCP#	OCCP#
	Health care workers	607(93.96)	3411(92.34)
	Non-health care workers	27(4.18)	195(5.28)
	MISS	12(1.86)	88(2.38)

*DE: death; DS: disability; HO: require hospitalization or prolongation of existing hospitalization; LT: life-threating; RI: required intervention to prevent permanent impairment/damage; OT: other serious medical events. #OCCP:reporter's type of occupation

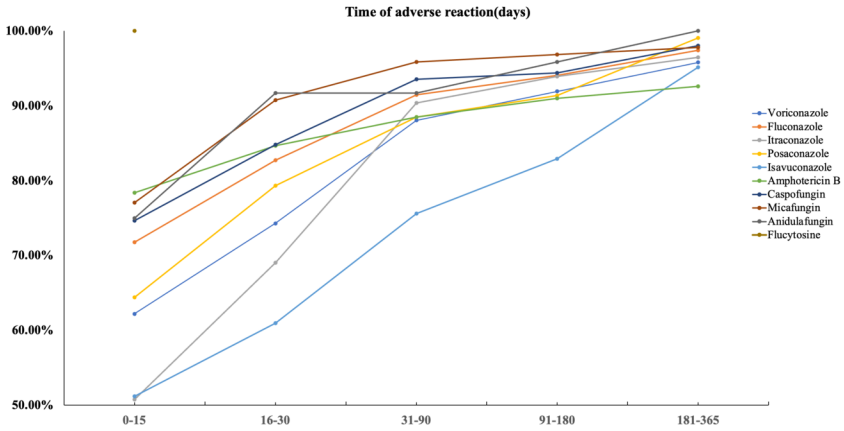


Fig.1 Cumulative event time (%) of hepatic events since the initiation of voriconazole and the control drugs

3.2 Signal values associated with hepatic dysfunction at SOC level

For the specific comparisons, there was a strong signal for increased hepatic dysfunction risk, when comparing voriconazole with the full database (**Fig.2)** , the ROR was 6.82 (95% CI 6.26-7.42). Comparing to the other antifungal drugs, voriconazole significantly increased the risk of hepatic dysfunction compared with fluconazole, isavuconazole and amphotericin B, with the RORs 2.19 (95% CI 1.94-2.47), 2.31 (95% CI 1.66-3.33) and 1.26 (95% CI 1.08-1.48), respectively. Analysis showed that voriconazole was not associated with a higher risk of hepatic dysfunction compared with itraconazole, posaconazole, caspofungin, micafungin, anidulafungin and 5-fluorocytosine (RORs 1.06 (95% CI 0.88-1.28), 1.08 (95% CI 0.89-1.30), 0.81 (95% CI 0.68-0.96), 0.75 (95% CI 0.62-0.90), 1.50 (95% CI 0.94-2.39), 1.00 (95% CI 0.44-2.27), respectively).

3.3 Signal values associated with hepatic dysfunction at PT level

In the secondary outcomes for the high frequency reporting of hepatic dysfunction events associated with voriconazole, the RORs (95% CI) for hepatic function abnormal, cholestasis, alanine aminotransferase increased, blood alkaline phosphatase increased, aspartate aminotransferase increased, liver function test abnormal, gamma-glutamyl transferase increased, liver disorder, hepatocellular injury, blood bilirubin increased were 19.17 (95% CI 15.54-23.63), 37.03 (95% CI 29.95-45.78), 8.59 (95% CI 6.71-11.00), 21.96 (95% CI

17.14-28.13), 10.17 (95% CI 7.91-13.08), 17.10 (95% CI 13.27-22.04), 20.89 (95% CI 16.11-27.09), 9.23 (95% CI 7.02-12.14), 18.81 (95%CI 14.26-24.81), 13.32 (95% CI 9.92-17.88), respectively (**Fig.3**).

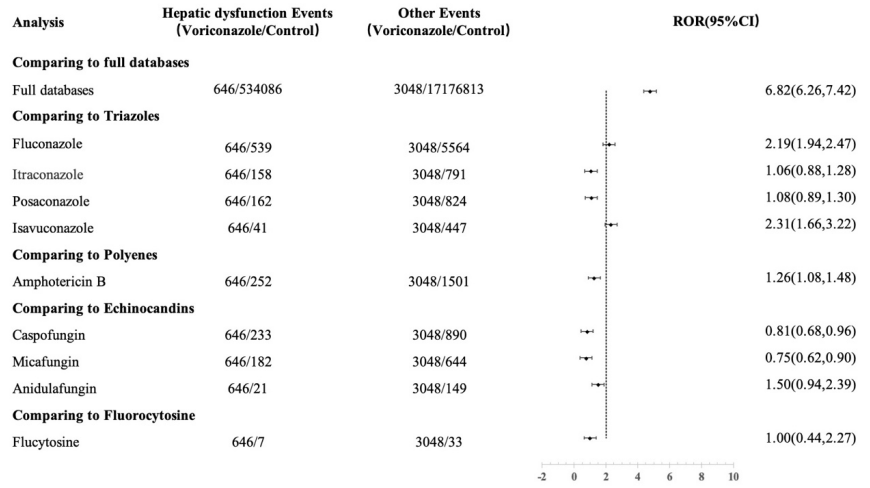
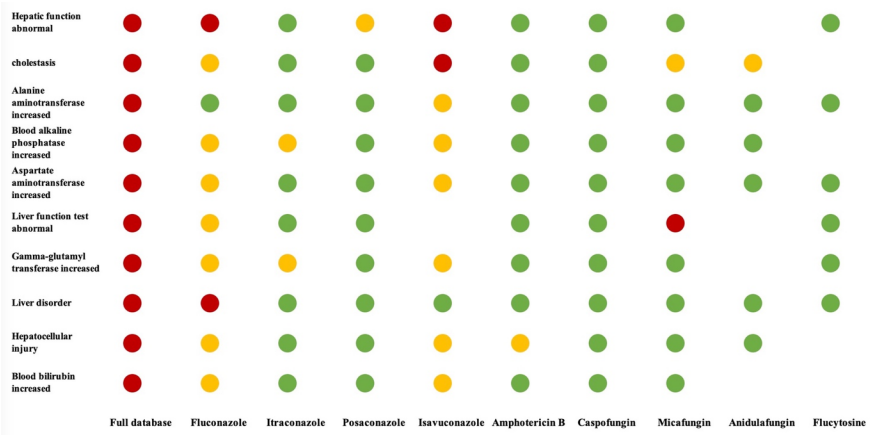


Fig.2 Overall hepatic dysfunction signals and RORs comparing voriconazole with the full database and other antifungal drugs



ROR [?] 5 2 [?] ROR $<$ 5 ROR $<$ 2

Fig.3 Subgroup analysis of different hepatic dysfunction events in voriconazole and other antifungal drugs

4. DISCUSSION

The main objective of this retrospective pharmacovigilance study is to investigate the hepatic dysfunction events of voriconazole, based on the real-world data records involved 73 quarters of the FAERS. Among our study we found that all the top ten frequency ADEs are strong correlation signal when compared with the full database.

In our study, 62.20% of patients developed hepatic dysfunction in 15 days of voriconazole use. The median time to event of the hepatic dysfunction events was 8 (IQR 2-28) days. We suggest health professionals

be aware of the potentially risk of voriconazole and monitor hepatic function during the first 15 days of voriconazole use.

Voriconazole remains the drug of choice for primary therapy of IA, with liposomal amphotericin B and the newly licensed agent isavuconazole considered alternatives [1]. Combination therapy with mold-active triazoles and echinocandins has been used with the hope of improving outcomes over monotherapy, especially in the setting of refractory disease [11]. Therefore, our study also did a comparison of voriconazole with the other antifungal drugs. In analyses stratified on the triazole antifungal drugs, an increased hepatic dysfunction event reporting was found in voriconazole when compared with fluconazole and isavuconazole, with the RORs (the lower limit of ROR 95% CI $>$ 1) 2.19 (95% CI 1.94-2.47), 2.31 (95% CI 1.66-3.33), respectively. A randomized, non-inferiority trial found that compared to voriconazole, isavuconazole was associated with a lower hepatotoxicity [12]. When comparing voriconazole with amphotericin B, there was a signal of high frequency of reporting hepatic dysfunction event with ROR (95% CI) 1.26 (1.08, 1.48). An observational study found that compared to amphotericin B, voriconazole was significantly associated with hepatotoxicity [p <0.0002; Odds Ratio=22.2 for voriconazole (95% CI, 4.3-116)] [13].

In analyses stratified on comparing to echinocandins, no signal of increased hepatic dysfunction event reporting was found (ROR<1). In previous studies, the echinocandins were considered to have a lower hepatotoxicity when compared with triazoles [14]. A network meta-analysis and systematic review on adverse reactions of antifungal drugs also showed that caspofungin was more significantly associated with a lower incidence of hepatobiliary disorders [15]. Whereas in the real word study, the results showed that echinocandins exhibited a higher hepatotoxicity which are consistent with our findings [16,17]. The risk of developing liver injury and possible hepatic dysfunction by an antifungal agent depends on several factors including underlying hepatic disease, echinocandins were considered as second-line or salvage therapy or antifungal combined therapy when monotherapy is not effective [18,19]. Since echinocandins can be used in patients with liver damage themselves, their related liver damage will be higher than the actual liver damage caused by voriconazole, which is also a shortcoming of this study.

In our hospital, the patient population is mainly liver transplantation and HIV infection, which are the main risk factors of invasive fungal infection. Therefore, precise treatment of invasive fungal infections is crucial in reducing mortality. Since voriconazole is the primary therapy for invasive aspergillosis, especially in immunocompromised patients, some clinical trials showed that supratherapeutic concentrations are correlated with an increased risk of hepatic toxicity [20,21]. Thus, voriconazole TDM is of paramount importance in patients with pre-existing liver disease, since the drug is extensively metabolized by the liver and this population is more difficult to tolerate a deterioration of hepatic function due to voriconazole-induced liver injury [22,23]. In our real word study based on the FAERS, we can't get the concentration of voriconazole, which is another limitation of this study.

There are inherent limitations with disproportionality analysis methods based on FAERS data. Firstly, the inherent nature of the FAERS which does not allow causality assessment between drug and AE. Secondly, concomitant drugs have not been considered, we will perform relevant drug interaction research in the future. Lastly, due to lack of the patient's underlying disease status, we did not consider the effect of disease factor which could be an important factor in hepatic abnormal events. Despite these drawbacks, the sample size of is enormous, the prevalence and risk of hepatic dysfunction and other AEs caused by voriconazole need to be further explored in prospective RCT studies.

5. CONCLUSION

In our article, we observed strong signals of higher frequency of reporting hepatic dysfunction events associated with voriconazole in the events of hepatic function abnormal. The median time to event of the hepatic dysfunction events were 8 days. Most hepatic related adverse events appeared within the first 15 days since the initiation of voriconazole administration. Moreover, an increased hepatic dysfunction event reporting was found in voriconazole when compared with fluconazole, isavuconazole and amphotericin B. Whereas, in our study, we observed that echinocandins exhibited a higher hepatotoxicity, which is inconsistent with the

results of previous clinical studies and need further studies. In any case, since the risk of developing liver injury and possible hepatic dysfunction by an antifungal agent depends on several factors including underlying hepatic disease, close clinical and laboratory monitoring, including TDM for specific antifungal drugs, is essential in the majority of these patients in order to prevent or promptly recognize further deterioration of the hepatic function, thus avoiding unfavorable outcomes.

Data Availability Statement

The FDA adverse events data used to analysis in this study was downloaded from FDA adverse events reporting system database, which was open accessed from the https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. Those downloaded data used to support the findings of this study were also included within the **Supplementary Material** file.

Conflicts of interest

The authors declare that they are no conflicts of interest.

Author Contribution

JY contributed to the data analysis and writing original draft. LF contributed to the data processing. JC and XL contributed to the management of AEs. WL contributed to the supervision, writing reviewing, and editing of this paper. All authors contributed to the article approved the submitted version.

Supplementary Material

The Supplementary Material for this article can be found online. Table S1: Generic and brand names of antifungal agents, Table S2: Preferred Terms included in this study, Table S3: The RORs of voriconazole compared with the full database and the other antifungal drugs, Table S4: The adverse event signals of voriconazole and the RORs compared with Full database, Table S5: The top ten frequency PTs and RORs of voriconazole compared with the other antifungal drugs.

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