Hepatotoxicity and Acute Kidney Injury Associations with Itraconazole, Voriconazole and Posaconazole in the Treatment of Onychomycosis: A Pharmacovigilance Study of FDA Adverse Event Reporting System Data (FAERS)

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Approval

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Ethics Statement

This project does not involve any clinical trial or human participants, no animals were used.

Abstract

Infections caused by fungi typically affect the skin, nails, and lungs but they can also penetrate the skin, infect the organs and spread throughout the body but research has found that dermatophytosis of the toenails and fingernails, known as onychomycosis, is more challenging to treat with medication than fungal infections of other body parts. Due to their high cure rates and safety profiles, azole antifungals replaced topical treatments in treating onychomycosis. However, studies suggest these medicines cause Hepatotoxicity and Acute kidney injury. In this study information from the FAERS database is analyzed using a reporting odds ratio (ROR) to identify potential danger signs. Hepatotoxicity Reporting odds ratio for drug's were, Voriconazole 8.16 (6.29, 10.60) > Itraconazole 3.98 (1.99, 7.96) > Posaconazole 3.23 (1.62, 6.47). Additionally, Acute kidney Injury Reporting odds ratio for selected drug were, Voriconazole 0.46 (0.33, 0.65) > Posaconazole 0.37 (0.19, 0.71) > Itraconazole 0.10 (0.03, 0.40).

Keywords: Onychomycosis; FAERS; reporting odds ratio (ROR); Hepatotoxicity: Acute Kidney Injury

Dedication

Dedicated to my faculty members, family and friends

Acknowledgement

I would like to start by thanking Almighty Allah for giving me strength throughout this project and Dr. Mesbah Talukder, Professor, School of Pharmacy, Brac University, for being a constant guide and so supportive, kind, and motivating.

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List of Acronym

FAERS	FDA Adverse Event Reporting System
MedDRA	Medical Dictionary for Regulatory Activities
CI	Confidence Interval
ROR	Reporting Odds Ratio
FDA	Food and Drug Administration
SOC	System organ class
AKI	Acute Kidney Injury
SBECD	Sulpho-butyl ether beta cyclodextrin sodium
ADR	Adverse Drug Reaction
Css	Concentration of drug in plasma at steady state

Chapter 1

INTRODUCTION

1.1 Fungal Infection and Onychomycosis

Infections caused by fungi have increased in recent years have been threatening millions of lives globally. *Candida, Fusarium,* and *Aspergillus* are prevalent fungi responsible for these diseases. Many fungal infections are dermatophyte-caused infections of the skin and nails including infections of nails, worms of the scalp, and athlete's foot. Verbal and sexual mucosal infections are widespread, especially vulvovaginal candidiasis. In contrast, invasive fungal infections are uncommon yet have substantial fatality rates (Mosallam et al., 2022). Infections caused by fungi typically affect the skin, nails, and lungs, but they can also penetrate the skin, infect the organs, and spread throughout the body. In contrast, research has found that dermatophytosis of the toenails and fingernails, known as onychomycosis, is more challenging to treat with medication than fungal infections of other body parts (Elewski, 1998). This is linked to the tough, strong nail plate and sluggish nail thickening, along with the considerably lower potency of initial pharmacologic medication. Furthermore, several studies have found that the prevalence of onychomycosis increases with age. Inadequate peripheral circulation, diabetes, recurrent nail injury, and extended contact with pathogenic fungus could all be contributing factors. In addition, there are four distinct forms of onychomycosis that are distinguished from one another by their clinical manifestations and their vectors of invasion (Elewski, 1998). Initially, the most common kinds of onychomycosis are Distal subungual onychomycosis. This condition may be recognized by the presence of an invasion of either the nail bed or lower part of nail plate, starting at the hyponychium and moving forward. Secondly, proximal subungual type is an infrequent variant that occurs when organisms invade the nail

unit through the keratin, puncture the newly formed nail plate, and spread downstream. Thirdly, white superficial onychomycosis develops when fungi penetrate the nail plate's superficial layers directly. Lastly, complete dystrophic onychomycosis is the medical name for severe nail disease. As fungi are responsible for approximately fifty percent of all nail dystrophies, the clinical features of dystrophic nails should arouse the clinician's diagnosis of onychomycosis. In fact, utilizing proper diagnostic methods, such as microscopic examination and fungal culture, is essential for ensuring accurate therapy and diagnosis (Elewski, 1998).

1.2 Current Treatment Strategies for Fungal Infection and Onychomycosis

Anti-fungal medication is used to treat fungal infections and the specific anti-fungal medication that is used is selected on the basis of the type of fungus that is responsible for the infection. Medications may be administered sublingually, topically or orally. Those with sepsis due to a fungal infection are given antifungal medications intravenously. There are various antifungal drugs currently available for treating fungal infections. The majority of these substances have significant systemic adverse effects because of the physicochemical parameters they possess as well as the high profile of toxicity they provide. In general, antifungals are often fungistatic or fungicidal, depending on their mode of action. Fungistatic medications restrict the development of fungi, whereas fungicidal drugs kill them. In addition, their chemical structure classifies them as azoles, polyene, echinocandin, allylamine, etc. Polyenes are ancient antifungals, whereas Nystatin is a potent antifungal polyene drug against fungi. Amphotericin-B is an antifungal polyene that combats Candida. On the contrary, azole antifungals restrict cell membrane synthesis with lanosterol-to-ergosterol enzyme inhibition. Finally, Echinocandins are Aspergillus antifungals. It is used as a secondary treatment alongside other antifungal (Mosallam et al., 2022).

Overall, among these drugs Fluconazole, Itraconazole, and Terbinafine are three recently developed antimycotic agents with significant cure rates and notable safety profiles. Furthermore, the short treatment intervals and inconsistent dose schedules are expected to enhance compliance and reduce onychomycosis therapy costs. Traditionally topical agents like imidazole's and allylamines were used by the physician but they were not that much effective because they can't get into the complete nail unit and kill the spores (Elewski, 1998).

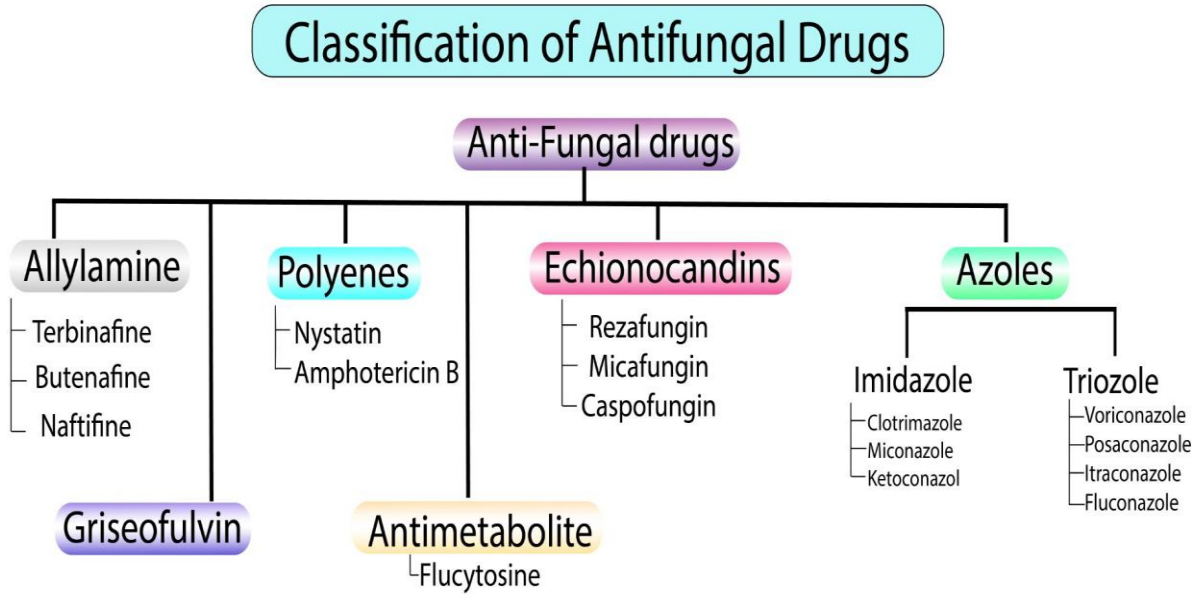

Figure 1: Classification of the Antifungal Drug's

1.3 Safety and Efficacy of Voriconazole, Itraconazole and Posaconazole

"Onychomycosis could well be controlled with a regular dose of 100–200 milligrams of Itraconazole (SM & Clissold, 1989)". For tinea corporis, it takes two weeks, for tinea pedis, it takes 4 weeks; for tinea capitis, it takes 4–8 weeks; and for onychomycosis, it takes 3–6 months. On the other hand, Voriconazole tablets is marketed under both its generic and brand names as 50 milligrams and 200 milligrams also in the form of oral suspension, and an injection. Additionally, severe infection caused by fungi are typically treated via intravenous voriconazole which is 4 to 6 milligrams per kg in every twelve hours for three to ten days, continued by oral formulations of the medicine (Health, 2017). Whereas, Posaconazole is currently available in three forms: an oral suspension, a tablet with a slow release of one hundred milligrams, and an intravenous formulation which is 18 milligrams per milliliter (Chen et al., 2020). In terms of efficacy toenails treated with Itraconazole have a 54% mycological cure rate, with a 14% full cure rate and complete remission rates. On the other hand, the rates of remission of 200 mg Posaconazole are around twenty-four weeks and around fifty percent (Gupta et al., 2020). Besides, a detailed study tried to find out the efficacy as well as safety of Voriconazole in 100 clinically identified dermatophytes at Zainul Haque Sikder Women's Medical College's skin outpatient department from August 2018 to August 2019. In fact, 80% of 100 patients were entirely cured, 15% were partially cured, and 5% were resistant to Voriconazole, a safer and more effective dermatophytosis treatment (Kafi et al., 2020). Finally, Posaconazole and Itraconazole inhibit the CYP3A4 hepatic enzyme and increase medication concentrations processed by this pathway. "Voriconazole levels are lowered if anyone takes Rifampin or long-acting barbiturates with it (Kafi et al., 2020)".

1.4 Relation to Voriconazole, Itraconazole and Posaconazole with Hepatotoxicity

In 11–19% of Voriconazole users, serum aminotransferase levels briefly increase. In most cases, these elevations do not produce any symptoms and resolve on their own; nonetheless, approximately 1% of patients must cease taking Voriconazole because their ALT levels increased. Clinical voriconazole hepatotoxicity is unknown. The drug's capacity to modify human sterol production may be related. For cytochrome P450 enzymes Voriconazole seems to be a substrate, which can elevate plasma levels of other drugs processed by these enzymes and induce toxicity (Health, 2017). Furthermore, lethargy and jaundice occur 1–6 months after starting Itraconazole. Sterol synthesis and P450 enzyme inhibition by Itraconazole may cause hepatotoxicity. As a potent CYP3A4 inhibitor, it can increase or decrease plasma levels of other drugs, increasing toxicity and efficacy (Health, 2017). Finally, Posaconazole raises liver enzymes, hyperbilirubinemia, and hepatocellular damage (Greer, 2007). It's ability to alter human sterol synthesis may explain it. Posaconazole inhibits CYP3A4, which can induce significant toxic effects and cross reactivity among drugs. Also, plasma level elevation of other P450-metabolized drugs occurs (Health, 2017).

1.5 Relation to Voriconazole, Itraconazole and Posaconazole with Nephrotoxicity

Oral Posaconazole has no intrinsic or mechanism-based nephrotoxicity, hence patients with reduced renal function do not need dose adjustments. However, the intravenous carrier sulfobutyl ether-cyclodextrin is removed by glomerular filtration and may accumulate in renal cells, therefore it should only be recommended to patients with moderate to severe renal illness after thorough risk-benefit analysis. On the other hand, Itraconazole and Voriconazole safety are well-known. Like other triazoles, they are well-tolerated and have no inherent

nephrotoxicity (Tragiannidis et al., 2021). However, in a recent study, individuals with acute renal failure who were treated with Voriconazole intravenously (IV) with dialysis therapy built up sulpho butyl ether beta cyclodextrin sodium in their bodies. Patients who have a creatinine clearance (CrCl) that is lower than 50 ml/min have an increased risk of having SBECD build up in their bodies (Kiser et al., 2015).

1.6 Voriconazole

Voriconazole is a triazole of the second generation that is effective against a wide variety of fungus. The most significant benefit of the medication is that it eradicates all prevalent kinds of *Aspergillus*. It is the initial medication used to treat invasive aspergillosis. In contrast, it is ineffective against Mucor mycosis, which is caused mostly by *Rhizopus, Mucor,* and *Basidia* species (Sandherr & Maschmeyer, 2011).

Initially, after two hours of ingestion, the oral bioavailability is greater than 90%. Food retards digestion and decreases bioavailability by 22%. In fact, it is better to take Voriconazole without eating. After 5-7 days of numerous oral doses, Voriconazole concentrations reach steady-state levels. However, loading doses decrease the steady-state duration to 1-2 days. In intravenous and oral tests, maximum concentration of drug and area under the curve increased in a dose-dependent process (Sandherr & Maschmeyer, 2011). Additionally, Voriconazole has a high distribution volume shows that it has a broad extracellular along with intracellular distribution. In the research, "the steady-state volume of distribution is reported to range from 2 liter per kg to 4.6 liter per kg (Theuretzbacher et al., 2006)". Furthermore, "Voriconazole is metabolized to voriconazole N-oxide by a sequence of reactions mediated by CYP2C19. Also contributing are CYP3A4, CYP2C9, and flavin-containing monooxygenase family members (Barbarino et al., 2017)". Nonetheless, the FMO family mediates only 25% of the total voriconazole metabolism. In addition, Voriconazole is also metabolized by hydroxylating its methyl group

and fluoropyrimidine ring (Barbarino et al., 2017). Coadministration of rifabutin and voriconazole reduces voriconazole levels and raises rifabutin serum concentrations to toxic levels (Sandherr & Maschmeyer, 2011). Finally, the half-life of Voriconazole following oral or IV treatment is approximately 6 hours (Theuretzbacher et al., 2006). In the urine no more than two percent of the dose of Voriconazole is excreted, indicating that the most percentage of this medicine are removed by hepatic metabolism. Approximately 20% of the medication is excreted in the feces.

"In fungi, Voriconazole significantly inhibits 14-sterol demethylase enzyme which is basically cytochrome P450-dependent. By doing inhibition it interferes with a crucial step in ergosterol production. The medication is roughly 250 times better potent against the fungal demethylase enzyme than it is against mammalian P450-dependent steroid hormone production (Donnelly & De Pauw, 2004)". The accumulation of 14-alpha methyl sterols causes a reduction in ergosterol, a crucial component in the development of the walls of fungi. It is believed that Voriconazole exerts its antifungal effects via altering the cellular structure of fungus (Saravolatz et al., 2003).

Voriconazole was given approval to treat invasive aspergillosis upon the findings of a substantial, international, randomly chosen treatment trial by comparing voriconazole with another antifungal drug amphotericin B (Herbrecht et al., 2002). Additionally, it was given approval to treat infections caused by *P. boydii* in people who can't take other antibiotics or whose infections are resistant to companions (Saravolatz et al., 2003).

Vision problems and rashes on the skin are two most reported side effect of Voriconazole but these are not major big problems and are not too serious (Saravolatz et al., 2003). Finally, Posaconazole raises liver enzymes, hyperbilirubinemia, and hepatocellular damage (Greer, 2007).

1.7 Itraconazole

Itraconazole is a triazole antifungal drug that can be taken orally and has a wide range of effects. Itraconazole is prescribed for approximately two weeks for the treatment of tinea corporis, one month for pedis, one or two months for capitis, and 3 to 6 months for onychomycosis (SM & Clissold, 1989).

Although different individual's absorption rate is not same but it is generally agreed that taking the drug with food increases absorption, so it should be taken after meal for maximizing therapeutic efficacy of Itraconazole. The concentrations of itraconazole in tissues is almost 10 times greater than plasma concentrations. Itraconazole could well be detectable at the surface of stratum corneum for approximately four weeks following administration (SM & Clissold,1989). Finally, a dose of hundred mg has almost half-life of 20 hours in healthy individuals. The liver metabolizes Itraconazole, which is then removed in urine and bile. At therapeutically effective doses, Itraconazole biotransformation may be saturable, resulting in nonproportionate rises in area under the curve for a given dose adjunct dose (SM & Clissold,1989).

According to studies, Itraconazole has been shown to interact with the substrate-binding site of the enzyme cytochrome P-450, that is compulsory for forming ergosterol. Azole nitrogen communicates with the hem iron found in yeast cytochrome, while the Itraconazole molecule's big hydrophobic part binds to the apoprotein component of the enzyme. As a consequence, the site of 14a-demethylation of ergosterol precursors is inhibited, which leads to an accumulation of lanosterol as well as a variety of 14a-methyl sterols (SM & Clissold,1989).

Non-comparative studies using itraconazole against cryptococcal meningitis suggest modest success if treatment is started early (Cauwenbergh et al., 1987). Additionally, Dermatophyte

(T. rubrum, T. mentagrophytes) yeast (*Candida albicans* and other *Candida sp*) onychomycosis have been cured by taking 100 to 200 milligrams of itraconazole once a day (SM & Clissold, 1989). Itraconazole is proved quite effective in treating the bloodstream's *candidiasis, chromomycosis, coccidioidomycosis, aspergillosis*, and *cryptococcosis*.

Isolated cases of hypokalemia have developed with four-month itraconazole treatment. Also, Itraconazole causes embryotoxicity and teratogenicity hence Pregnancy contraindication.

1.8 Posaconazole

The U.S. Food and Medication Administration has authorized Posaconazole, a fluorinated triazole antifungal drug (FDA). In fact, "currently, there are three formulations available: oral suspension of 40 milligrams per milliliter, a delayed-release tablet 100 milligrams, and also intravenous formulation 18 milligrams per milliliter (Chen et al., 2020)".

Food and dietary supplements make Posaconazole more soluble and slower down the rate at which the stomach empties. Higher gastro intestinal pH and Gastro intestinal motion make it harder for oral suspensions to be absorbed because they are less soluble and stay in the stomach for less time (Chen et al., 2020). Posaconazole's wide distribution suggests extravascular and tissue penetration (3–5). More than 95% of Posaconazole is albumin-bound (Greer, 2007). Furthermore, Posaconazole differs from other triazole antifungals in that the cytochrome P450 (CYP) pathway barely breaks it down. UGT1A4 is responsible for around 17% of glucuronidation, whereas the remainder is removed in its original form. Posaconazole could still be affected as a victim medicine by phenytoin and rifampin, which interact with UGT enzymes (Greer, 2007). Finally, Posaconazole is eliminated primarily by feces (66%). However, less than 1% of the parent chemical is eliminated by the kidneys. The half-life of Posaconazole is 25 to 35 hours (Greer, 2007).

Posaconazole blocks the enzyme lanosterol 14-demethylase from functioning and prevents ergosterol from being produced, a fungal cell membrane component. It further induces methylated sterol precursors to build up and reduce ergosterol in the membrane of cell. This degrades the fungal cell membrane and assist Posaconazole kill fungi.

Typically, it is employed when other azoles or amphotericin B either fail to work or are intolerable, it is used to treat *aspergillosis, fusariosis, chromoblastomycosis*, and *coccidioidomycosis* (Clark et al., 2015). Besides Posaconazole works against many *Mucorales* species much better than other azoles (Clark et al., 2015).

"Hemolytic uremic syndrome, adrenal insufficiency, pulmonary embolism, thrombotic thrombocytopenic purpura, and hypersensitivity responses are infrequent with Posaconazole. Additionally, Posaconazole and other triazole antifungals may prolong QT interval (Greer, 2007)". Also, Auditory and visual hallucinations are among the unusual neurologic adverse effects (Clark et al., 2015).

1.9 Comparison of Voriconazole, Itraconazole and Posaconazole's Pharmacokinetics

Table 1: Comparison of Voriconazole, Itraconazole and Posaconazole's Pharmacokinetics (Chen et al., 2020; Greer, 2017; Sandherr & Maschmeyer, 2011; Theuretzbacher et al., 2006)

Property	**Itraconazole**	**Voriconazole**	**Posaconazole**
Absorption	Absorption enhanced when the medicine is delivered with a meal, and this administration pattern is advised for maximizing therapeutic benefit.	Absorption decreases when the medicine is delivered with a meal and reduces bioavailability to a greater extent.	Food and nutritional supplements improve solubility and delay stomach emptying, increasing Posaconazole exposure
Tmax	4–5 hours	1–2 hours	4–5 hours
Distribution	Itraconazole could well be detectable in the stratum corneum for approximately four weeks following administration, reflecting its affinity for sebum and keratinocytes.	The fact that voriconazole has a large volume of distribution suggests that it has a broad distribution both extracellularly and intracellularly	Posaconazole accumulates in systemic tissues for instance, alveolar cell exposure is approximately 32 times greater than plasma exposure in healthy individuals who received 400 mg of Posaconazole suspension BID.
Protein binding	only 1% is unbound	less protein bound than the other two.	almost 10% is unbound to protein
Volume of distribution	11 L/kg	4.6 L/kg	1774 L

Bioavailability	50%–75%	>95%	not fixed
Metabolism	Hepatic: CYP3A4	Hepatic: CYP2C19, 2C9, 3A4.	Hepatic
Elimination half-life & route	35–64 hours <1% excreted unchanged in urine	6–24 hours <2% excreted unchanged in urine	Between 25 to 35 hours Less than one percent excreted through urine and sixty- six percent excreted in the feces(unchanged)

1.10 Pharmacodynamics (Mechanism of Action)

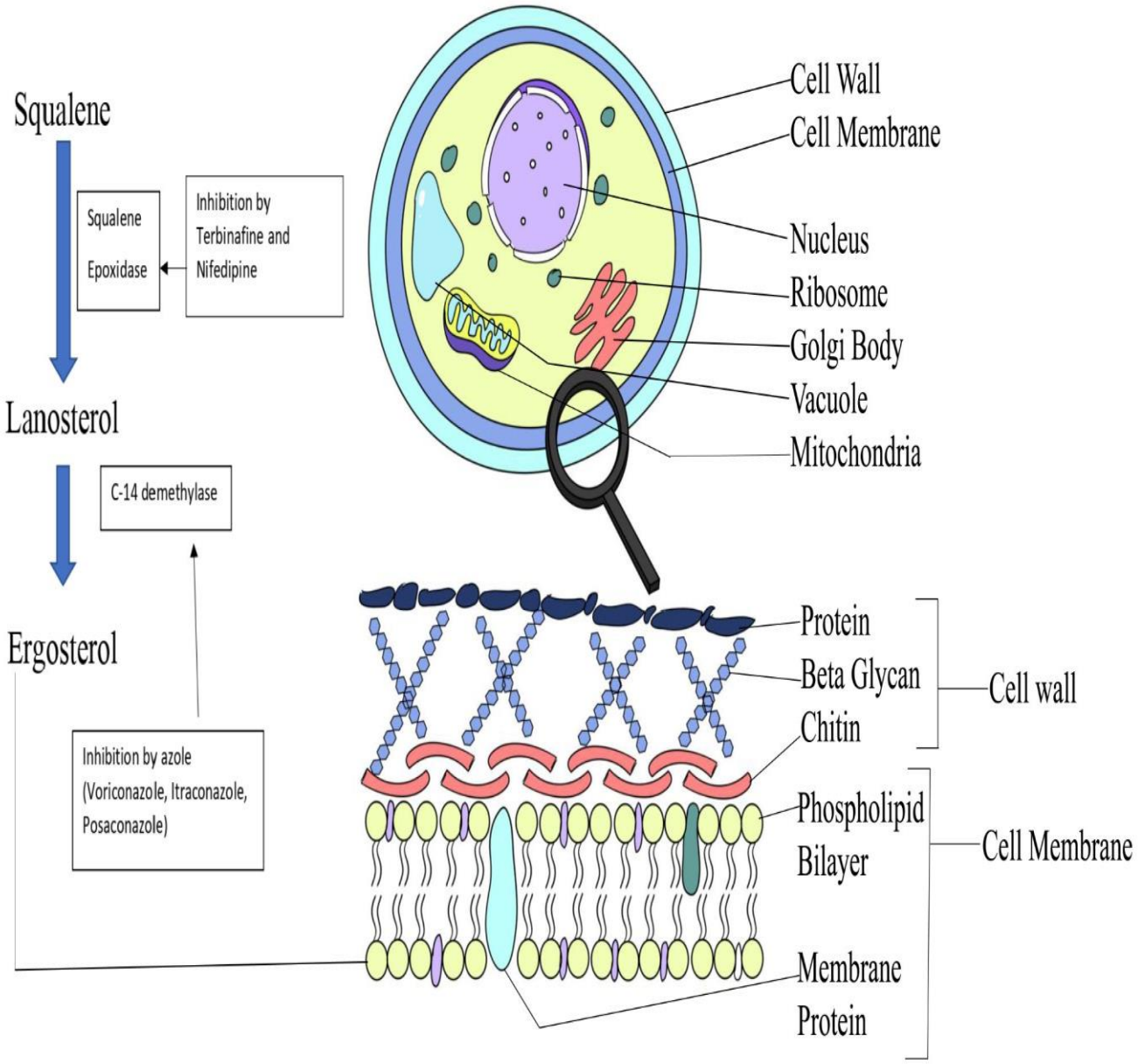

Figure 2: Mechanism of action of Voriconazole, Itraconazole & Posaconazole

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Chapter 2

Sources and Search Strategy

2.1 Data Source

The FDA Adverse Event Reporting System is a database which is accessible for all people and it comprises of all adverse event reports that are submitted to the Food & drug administration, USA. As it is an open database so no approval is needed to collect data from there. It is comprised of adverse event reports given by people associated with health system, product users, and companies who manufacture products in the US under FDA (Patek et al., 2020). The FAERS database includes various information about drug for example name of the drug, the ingredient that are used, the way of taking that drug and reaction information. Also has a key role in post-market drug surveillance when it comes to finding and describing drug- and device-related side effects. The intention of post-marketing drug monitoring systems is to reduce the probability of adverse medication responses in hospital and retail settings. Generally, spontaneous adverse event reporting approaches are employed. Due to the brief timeframe of treatment response and the limited number and diversification of the community being investigated, the information collected during the medication development process is often inadequate. Therefore, unexpected adverse drug responses cannot be traced to the medications being tested in drug development, since just only a few thousand participants are enrolled while only the most common side effects are identified (Khaleel et al., 2022). Information from the US FDA adverse event reporting system database was analyzed using a reporting odds ratio (ROR) to identify potential danger signs (FAERS). Additionally, Medical Dictionary for Regulatory Activities defined things based on system organ class (SOCs) and preferred terminology (PTs) (MedDRA).

2.2 Inclusion and Exclusion Criteria

The data reported to the international FAERS database between January 2016 -September 2022 was considered for this study. We removed any data when a number of additional substances of abuse were believed to be present. Using the case number, duplicate reports were omitted. By matching the age, gender, and event date, duplicate reports were eliminated in a second manner. We exclusively utilized the “Acute kidney injury" and "Hepatotoxicity" to find out cases of kidney and liver injury, respectively**.** For predicting the severity Isoniazid and Gentamicin's ROR was calculated because Isoniazidis known hepatotoxic and gentamicin is nephrotoxic drug.

2.3 Endpoints

The end points for this project are "Acute kidney injury" and "Hepatotoxicity”. The end points are specified using the MedDRA Preferred Terminologies.

2.4 Statistical Analysis

By calculating reporting odds ratios and their 95% confidence intervals for the reporting relationship among selected adverse effect with certain azole antifungal drug, disproportionality research was conducted. The Reporting odd ratio was estimated as the probabilities that a report was reported for that particular consequence versus the reports that did not indicate hepatotoxicity for a given medicine (Patek et al., 2020). "A claimed relationship is clinically meaningful if the lower threshold of the 95% confidence interval is greater than 1 (Patek et al., 2020)". A greater ROR indicated a better relationship between reporting Hepatotoxicity and Acute Kidney Injury with the specified medicine, Microsoft Excel 2016 and software R (version 4.2.1) were used to analyze the data.

Chapter 3

Results

3.1 Signal for (Hepatotoxicity & Acute Kidney Injury)

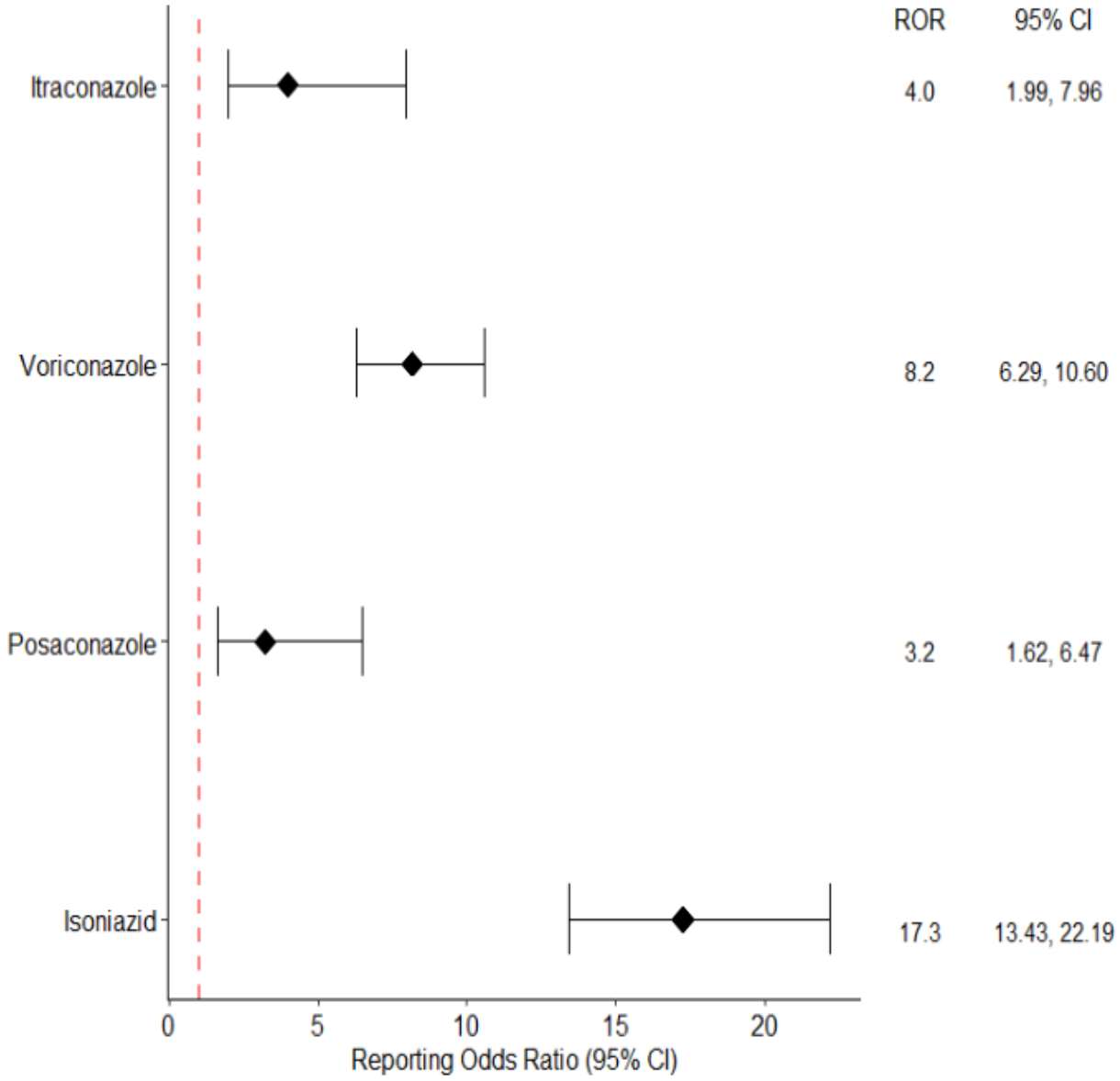

Figure 3: Forest Plot for Hepatotoxicity of Anti-fungal against the whole database (Isoniazid is used as a control)

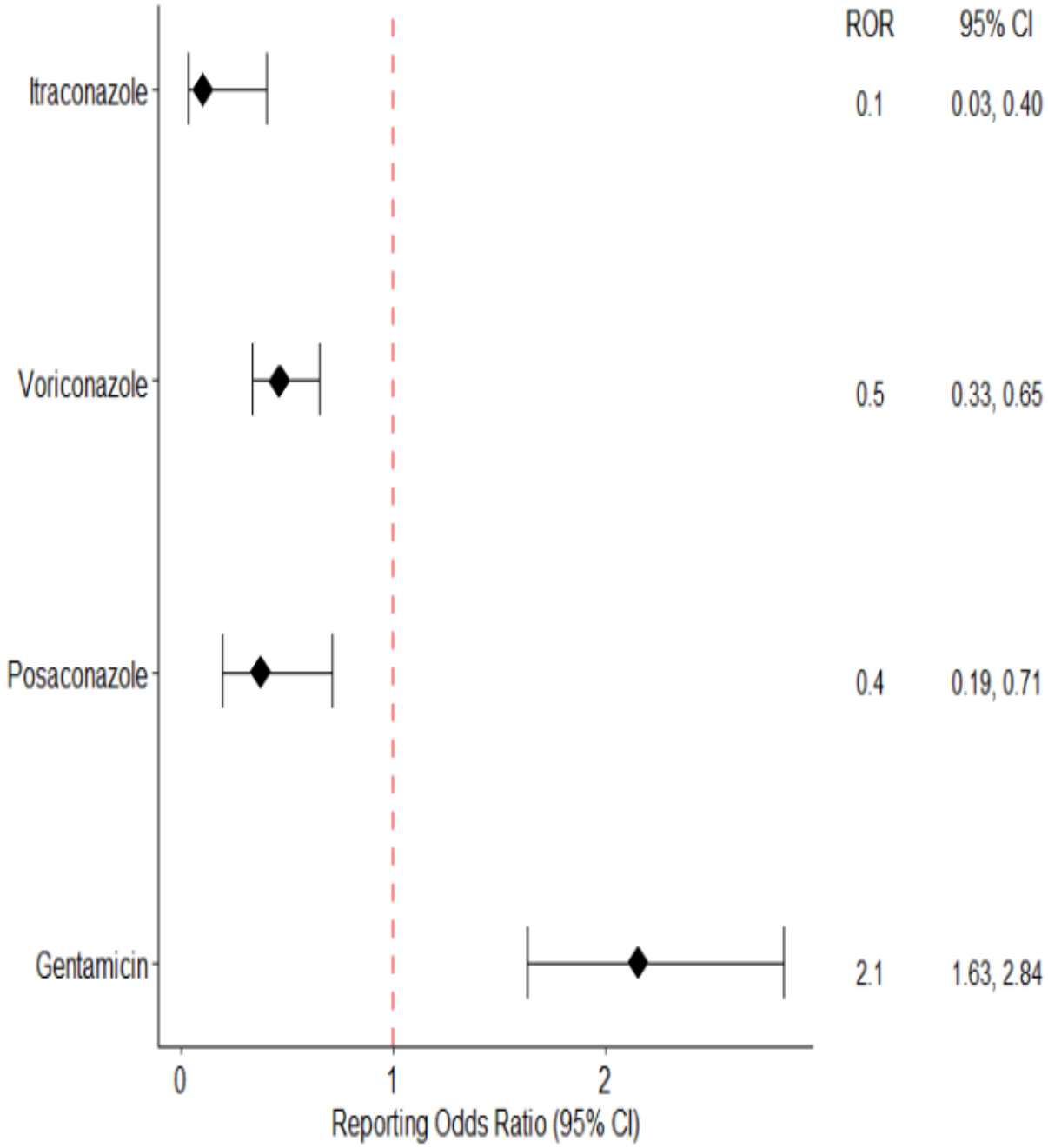

Figure 4; Forest Plot for Acute Kidney Injury of Anti-fungal against the whole database (Gentamicin is used as a control)

In terms of Itraconazole a total of 2789 reports (including 8 hepatotoxicity reports & 2 acute kidney injury) were reviewed after implementing the inclusion parameters. On the other hand, for voriconazole total 9755 reports (including 57 hepatotoxicity reports & 32 acute kidney injury) and for Posaconazole total 3429 reports (including 8 hepatotoxicity reports & 9 acute kidney injury) were considered. Hepatotoxicity Reporting odds ratio (95% Confidence interval) for drug's were, Voriconazole 8.16 (6.29, 10.60) > Itraconazole 3.98 (1.99, 7.96) > Posaconazole 3.23 (1.62, 6.47). Additionally, Acute kidney injury Reporting odds ratio (95% Confidence interval) for selected drug were, Voriconazole 0.46 (0.33, 0.65) > Posaconazole 0.37 (0.19, 0.71) > Itraconazole 0.10 (0.03, 0.40).

"A claimed relationship is clinically meaningful if the lower threshold of the 95% confidence interval is greater than 1 (Patek et al., 2020)". A greater ROR indicated a better relationship between reporting Hepatotoxicity and Acute Kidney Injury with the specified medicine. That means all the drugs are showing signal for hepatotoxicity and among them voriconazole is showing strongest signal (Figure 3). However, none of the drugs have shown signal for acute kidney injury (Figure 4). When compared to the incidence of hepatic adverse responses created by other medicines, the prevalence of isoniazid-induced adverse effects is quite significant. Approximately twenty percent of the total users had increased alanine amino transferase concentrations in their bloodstream (Hassan et al., 2015). On the other hand, the reported rates are 1.2 percent to 55 percent of overall gentamicin renal damage level, with majority of research reporting rates between 8% and 26% (Selby et al., 2009). Based on multiple studies they are known agents of hepatotoxicity and acute kidney injury. Assuming them as a control in this study, we also tried to make a comparison by calculating their ROR (95% Confidence interval) and found that Isoniazid is almost twice times more reported for hepatotoxicity and gentamycin almost five times more reported for acute kidney injury compared to Voriconazole.

Table 2: Reporting odd ratio based on the data reported to the international FAERS database between 2016 - 2022

Drug Name	**Cases Hepatotoxicity**	**Cases Acute kidney Injury**	**ROR (95% Cl) Hepatotoxicity**	**ROR (95% Cl) Acute kidney Injury**
Itraconazole	8	2	3.98 (1.99, 7.96)	0.10 (0.03, 0.40)
Voriconazole	57	32	8.16 (6.29, 10.60)	0.46 (0.33, 0.65)
Posaconazole	8	9	3.23 (1.62, 6.47)	0.37 (0.19, 0.71),
Isoniazid	62	×	17.26 (13.43, 22.19)	×
Gentamicin	×	50	×	2.15 (1.63, 2.84)

3.2 Discussion

This research's findings show that Voriconazole has a proportionately greater odds ratio (ROR) for Hepatotoxicity, followed by Itraconazole and Posaconazole. Even though Voriconazole has been linked to hepatotoxicity on a regular basis, the actual role and primary consequence relationship are yet unknown. Drug's concentration in the plasma is the most accurate indicator of both its efficacy and its toxicity. "A trough concentration of voriconazole that was greater than 3.0 mg/L was assessed to be hepatotoxic, while a plasma concentration of 0.5 mg/L was considered satisfactory (Tasleem & Cappell, 2019)". Nevertheless, the substantial steady-state concentration variability that is observed with Voriconazole poses a significant problem. Even though the usual dose was given to all of the participants in one trial, the Css of Voriconazole in the patient's blood ranged from 0 to 16.6 micrograms per milliliter. In addition, a different study found that this range was significantly more expansive (0.10–20 mg/L) (Tasleem & Cappell, 2019). Mainly Similar to the effects of other azole medications, treatment with Voriconazole can cause an increase in the activity of liver enzymes. Increasing levels of alanine aminotransferase and aspartate aminotransferase marked as the typical pattern; nevertheless, elevations in the levels of alkaline phosphatase is also observed in some cases. However the majority of patients have an asymptomatic increase of liver enzyme levels, there have been several cases identified who have severe hepatitis that poses a threat to their life (Saravolatz et al., 2003). A case report demonstrated that after failing Itraconazole, Fluconazole, Amphotericin B, and Flucytosine, ten years old with Human immune deficiency virus infection and acquired immune deficiency syndrome started Voriconazole for esophageal candidiasis. Serum enzymes raised after a day. Voriconazole was discontinued on day 7 due to rising aminotransferases. After quitting voriconazole, the patient's liver function declined rapidly. Even though she stopped taking her antiviral medicine, her liver cirrhosis got severe 28 days after she took voriconazole and led to liver failure, unconsciousness, and death (Health, 2017).

Our results also demonstrated there are no significant Acute kidney injury associations with Voriconazole, Itraconazole and Posaconazole. However, among them Voriconazole showed the maximum cases in FAERS database. There isn't much information about how much sulpho butyl ether beta cyclodextrin sodium is in the blood when voriconazole is given intravenously to people who don't have enough kidney function. According to current data, individuals with acute renal failure who were given voriconazole by IV and dialysis therapy built up sulpho butyl ether beta cyclodextrin sodium. Patients whose Clearance of creatinine is >50 ml/min are building SBECD in their bodies. SBECD proliferation in animal populations at dosages that are fifty times higher than those that are commonly supplied in human being. It has been associated to hepatic damage and glomeruli obstruction. In individuals whose creatinine clearance amount found >50 ml/min, it is strongly suggested that oral voriconazole be used rather than IV voriconazole (Kiser et al., 2015).

Chapter 4

Limitations

Using the FAERS database, it is not possible to figure out whether or not a medicine produced an adverse event. Due to the random and spontaneous character of ADR reporting, there is the potential for considerable bias. Attention from the media and the recent analysis in the journals about an ADR are also potential factors that could influence reporting habits. The relationship among a medication and an adverse drug response is complicated by the presence of disease complications and the simultaneous usage multiple drugs (Patek et al., 2020). Also, the submission of a report does not imply that its contents have been medically confirmed, nor does it constitute an admission by the reporter that the substance caused or contributed to the occurrence. Therefore, as consequence of the random intakes of data from several sources (such as people associated with health system, product users, and company who manufacture products) case report duplication is a known issue in the FAERS database. Although, in this research by using the case number, duplicate reports were omitted by us. Additionally, by matching the age, gender, and event date, duplicate reports were eliminated in a second manner. But duplication has been a big detrimental for FEARS database. All of these factors would affect the accuracy and dependability of the data processing if they were not adequately managed and reduced to the smallest extent possible. To generate a pure, homogenized, and regulated dataset that is suitable for use by any researcher, it is necessary to ensure a time-consuming multi-step processing of raw data. To achieve the desired outcome, qualified individuals will need to search the database as part of the entire process. FAERS's big enough sample size makes it appropriate for identifying unexpected and frequent drug-ADR associations (Patek et al., 2020).

Chapter 5

Conclusion

In our study, we confirmed three of azole antifungal (Voriconazole, Itraconazole and Posaconazole) having considerable reporting relationships with Hepatotoxicity. Between Voriconazole, Itraconazole and Posaconazole the drug showed the strongest hepatotoxicity signal is Voriconazole and Posaconazole had the least strong relationship with it. we also compared the severity of toxicity with a reference drug (Isoniazid) which is already established for Hepatoxicity. Similarly, this study tried to find the associations between the selected drug and Acute kidney injury. According to the data of FEARS database these drugs are not liable for causing acute kidney injury because none of them showed significant signal also have a significant difference in ROR value with a reference drug (Gentamicin).

Lastly, because there are limits to the data, the results from FAERS should be interpreted with care. Therefore, conducting additional research into this is important such as evaluating its clinical relevance also effect after patient take those drugs, so that we can better assist medical professionals in the safe prescription of voriconazole.

References

Abdulla-Hel Kafi, M., Akter, M., Khan, R., Shair Ahmed, S., Jonayed Hassan, M., Shariful Hassan, M., & Professor, A. (2020). Efficacy and Safety of Voriconazole in the treatment of resistant cases of Dermatophytosis. *Journal of ZHSWMC*, *2*(1).

Aoul, R., Erbrecht, H., Enning, A. W. D., Atterson, H. F. P., Ohn, J., Ennett, E. B., Eginald, R., Reene, E. G., Estmann, J. Ö.-W. O., Ern, I. V. K., Arr, I. A. M., Atricia, P., Ibaud, R., Ortholary, L. L., Ichard, R., Ylvester, S., Ubin, O. H. R., Ingard, R. W., Aul, P., … Roke, E. F. T. (2002). Voriconazole versus Amphotericin B for Primary Therapy of Invasive Aspergillosis. *Https://Doi.Org/10.1056/NEJMoa020191*, *347*(6), 408–415. https://doi.org/10.1056/NEJMOA020191

Barbarino, J. M., Obeng, A. O., Klein, T. E., & Altman, R. B. (2017). PharmGKB Summary: Voriconazole Pathway, Pharmacokinetics. *Pharmacogenetics and Genomics*, *27*(5), 201. https://doi.org/10.1097/FPC.0000000000000276

Cauwenbergh, G., de Doncker, P., Stoops, K., de Dier, A. M., Goyvaerts, H., & Schuermans, V. (1987). Itraconazole in the Treatment of Human Mycoses: Review of Three Years of Clinical Experience. *Reviews of Infectious Diseases*, *9*(Supplement_1), S146–S152. https://doi.org/10.1093/CLINIDS/9.SUPPLEMENT_1.S146

Chen, L., Krekels, E. H. J., Verweij, P. E., Buil, J. B., Knibbe, C. A. J., & Brüggemann, R. J. M. (2020). Pharmacokinetics and Pharmacodynamics of Posaconazole. *Drugs 2020 80:7*, *80*(7), 671–695. https://doi.org/10.1007/S40265-020-01306-Y

Clark, N. M., Grim, S. A., & Lynch, J. P. (2015). Posaconazole: Use in the Prophylaxis and Treatment of Fungal Infections. *Seminars in Respiratory and Critical Care Medicine*, *36*(5), 767–785. https://doi.org/10.1055/S-0035-1562902/ID/JR01154-36

Courtney, R., Pai, S., Laughlin, M., Lim, J., & Batra, V. (2003). Pharmacokinetics, safety, and tolerability of oral Posaconazole administered in single and multiple doses in healthy adults. *Antimicrobial Agents and Chemotherapy*, *47*(9), 2788–2795. https://doi.org/10.1128/AAC.47.9.2788-2795.2003/ASSET/123AA290-4DF9-4647-8639-85662062A2C7/ASSETS/GRAPHIC/AC0930949005.JPEG

Donnelly, J. P., & de Pauw, B. E. (2004). Voriconazole—a new therapeutic agent with an extended spectrum of antifungal activity. *Clinical Microbiology and Infection*, *10*(SUPPL. 1), 107–117. https://doi.org/10.1111/J.1470-9465.2004.00838.X

Elewski, B. E. (1998). Onychomycosis: Pathogenesis, diagnosis, and management. *Clinical Microbiology Reviews*, *11*(3), 415–429. https://doi.org/10.1128/CMR.11.3.415/ASSET/CED1A021-4E22-4BBD-A6F9-A6419D481634/ASSETS/GRAPHIC/CM0380016009.JPEG

Espinel-Ingroff, A. (1998). In Vitro Activity of the New Triazole Voriconazole (UK-109,496) against Opportunistic Filamentous and Dimorphic Fungi and Common and Emerging Yeast Pathogens. *Journal of Clinical Microbiology*, *36*(1), 198–202. https://doi.org/10.1128/JCM.36.1.198-202.1998

Greer, N. D. (2017). Posaconazole (Noxafil): A New Triazole Antifungal Agent. *Https://Doi.Org/10.1080/08998280.2007.11928283*, *20*(2), 188–196. https://doi.org/10.1080/08998280.2007.11928283

Gupta, A. K., Stec, N., Summerbell, R. C., Shear, N. H., Piguet, V., Tosti, A., & Piraccini, B. M. (2020). Onychomycosis: a review. *Journal of the European Academy of Dermatology and Venereology*, *34*(9), 1972–1990. https://doi.org/10.1111/JDV.16394

Hassan, H. M., Guo, H. L., Yousef, B. A., Luyong, Z., & Zhenzhou, J. (2015a). Hepatotoxicity mechanisms of isoniazid: A mini-review. *Journal of Applied Toxicology*, *35*(12), 1427–1432. https://doi.org/10.1002/JAT.3175

Hassan, H. M., Guo, H. L., Yousef, B. A., Luyong, Z., & Zhenzhou, J. (2015b). Hepatotoxicity mechanisms of isoniazid: A mini-review. *Journal of Applied Toxicology*, *35*(12), 1427–1432. https://doi.org/10.1002/JAT.3175

Hoofnagle, J. H. (2013). LiverTox: A Website on Drug-Induced Liver Injury. *Drug-Induced Liver Disease*, 725–732. https://doi.org/10.1016/B978-0-12-387817-5.00040-6

Johnson, L. B., & Kauffman, C. A. (2003). Voriconazole: A new triazole antifungal agent. *Clinical Infectious Diseases*, *36*(5), 630–637. https://doi.org/10.1086/367933/2/36-5-630-TBL003.GIF

Khaleel, M. A., Khan, A. H., Ghadzi, S. M. S., Adnan, A. S., & Abdallah, Q. M. (2022). A Standardized Dataset of a Spontaneous Adverse Event Reporting System. *Healthcare 2022, Vol. 10, Page 420*, *10*(3), 420. https://doi.org/10.3390/HEALTHCARE10030420

Kiser, T. H., Fish, D. N., Aquilante, C. L., Rower, J. E., Wempe, M. F., MacLaren, R., & Teitelbaum, I. (2015). Evaluation of sulfobutylether-β-cyclodextrin (SBECD) accumulation and voriconazole pharmacokinetics in critically ill patients undergoing continuous renal replacement therapy. *Critical Care*, *19*(1), 1–9. https://doi.org/10.1186/S13054-015-0753-8/TABLES/4

Mosallam, S., Albash, R., & Abdelbari, M. A. (2022). Advanced Vesicular Systems for Antifungal Drug Delivery. *AAPS PharmSciTech*, *23*(6), 1–11. https://doi.org/10.1208/S12249-022-02357-Y/FIGURES/3

Patek, T. M., Teng, C., Kennedy, K. E., Alvarez, C. A., & Frei, C. R. (2020). Comparing Acute Kidney Injury Reports Among Antibiotics: A Pharmacovigilance Study of the FDA Adverse Event Reporting System (FAERS). *Drug Safety*, *43*(1), 17–22. https://doi.org/10.1007/S40264-019-00873-8/METRICS

Pitisuttithum, P., Negroni, R., Graybill, J. R., Bustamante, B., Pappas, P., Chapman, S., Hare, R. S., & Hardalo, C. J. (2005). Activity of posaconazole in the treatment of central nervous system fungal infections. *Journal of Antimicrobial Chemotherapy*, *56*(4), 745–755. https://doi.org/10.1093/JAC/DKI288

Sandherr, M., & Maschmeyer, G. (2011). Pharmacology and metabolism of voriconazole and posaconazole in the treatment of invasive aspergillosis - Review of the literature. *European Journal of Medical Research*, *16*(4), 139–144. https://doi.org/10.1186/2047-783X-16-4-139/TABLES/4

Selby, N. M., Shaw, S., Woodier, N., Fluck, R. J., & Kolhe, N. v. (2009). Gentamicin-associated acute kidney injury. *QJM: An International Journal of Medicine*, *102*(12), 873–880. https://doi.org/10.1093/QJMED/HCP143

SM, G., & Clissold, S. (1989). Itraconazole. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in superficial and systemic mycoses. Drugs, 37, 310-344

Tasleem, S. H., & Cappell, M. S. (2019). Voriconazole-Induced Hepatotoxicity Presenting With Severe Hepatic Encephalopathy After Liver Transplantation. *ACG Case Reports Journal*, *6*(3), e00010. https://doi.org/10.14309/CRJ.0000000000000010

Theuretzbacher, U., Ihle, F., & Derendorf, H. (2006). Pharmacokinetic/pharmacodynamic profile of voriconazole. *Clinical Pharmacokinetics*, *45*(7), 649–663. https://doi.org/10.2165/00003088-200645070-00002/METRICS

Tragiannidis, A., Gkampeta, A., Vousvouki, M., Vasileiou, E., & Groll, A. H. (2021). Antifungal agents and the kidney: pharmacokinetics, clinical nephrotoxicity, and interactions. *Https://Doi.Org/10.1080/14740338.2021.1922667*, *20*(9), 1061–1074. https://doi.org/10.1080/14740338.2021.1922667