Switching antifungals drugs within the triazole drug class: a potential treatment approach to drug-related hepatotoxicity

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Abstract

There are limited data on the best approach to managing azole-induced hepatotoxicity. One described approach is switching between different triazole agents to prevent the need for intravenous therapy. This case series describes the outcomes of this approach in seven children. The most common azole switch was voriconazole to fluconazole (3/7), followed by fluconazole to voriconazole (2/7). One child each switched from voriconazole to itraconazole, and posaconazole to fluconazole. Of the seven cases, five had Grade 3 liver injury and two had Grade 2 liver injury. These LFT abnormalities were deemed as 'possibly' in four cases, and 'probably' in three cases to be related to the first azole antifungal as per the Naranjo criteria. All had improvement in their LFT abnormalities after the switch to an alternative azole antifungal. These data suggest that switching azole antifungals offers a potential treatment approach to azole-induced hepatotoxicity.

Introduction

Invasive fungal infections are an important cause of morbidity and mortality in children. Triazole antifungal agents are increasingly used for prophylaxis and treatment of mould infections in paediatric oncology settings, however, confer a risk of azole-induced hepatotoxicity (AIH), particularly when concomitantly administered with other hepatotoxic medications. There are limited data on the best approach to AIH. As triazole antifungal agents are the only antifungal formulation available in oral form for children, one described approach is switching between different triazole agents within the azole class to prevent the need for intravenous (IV) therapy. To date, there have only been three case reports and one retrospective audit in adults of this approach[1-4]. This study therefore aimed to describe the outcomes of switching triazole antifungal agents for AIH in children.

Methods

Using an electronic medical record report in Epic, we identified children aged 0 to 18 years who switched from one triazole antifungal to a different triazole while an inpatient at a tertiary referral pediatric hospital, The Royal Children's Hospital Melbourne (RCH), Australia over a five-year period (Nov 2016 to Oct 2021). Children were included if they had: received [?]48 hours of antifungal therapy with the first triazole; had abnormal liver function tests (LFTs) consistent with Common Terminology Criteria for Adverse Events (CTCAE)[5] Grade 2 liver injury or above prior to switching triazole antifungals; the first triazole antifungal was assessed as a possible or probable cause of the LFT abnormality as per the Naranjo criteria by a paediatric clinical pharmacologist (AG)[6]; the child received the second triazole antifungal within 48 hours of cessation of the first drug and the abnormal LFTs improved after the switch. Children were included only if the results of their LFTs were available at baseline (prior to azole therapy), at the end of their first triazole antifungal course, and within 2 to 14 days after the antifungal switch and end of therapy.

Clinical data on patient demographics, medical comorbidities, antifungal agents received, and other hepatotoxic medications administered were collected. Concomitant hepatotoxic medications and the probability of

effect on deranged LFTs were identified as per LiverTox[7]. Ethics approval was obtained from RCH human research ethics committee (HREC 76476).

Results

Over the five-year period, seven cases fulfilled the inclusion criteria. The median age was 7.3 years (range 4.2-16.6) and 6/7 were male (Table 1). Four had a hematological malignancy, two had a primary immunodeficiency and five were hematopoietic stem cell transplant recipients (HSCT) (Table 1). The most common azole switch was voriconazole to fluconazole (3/7), followed by fluconazole to voriconazole (2/7). One child each switched from voriconazole to itraconazole, and posaconazole to fluconazole.

Of the seven cases, five had Grade 3 liver injury and two had Grade 2 liver injury. All children had an elevated Gamma-glutamyl Transferase (GGT) level (Grade 2 to 3) and three had Grade 2 Alanine Aminotransferase (ALT) abnormalities (Table 1; Figure 1). These LFT abnormalities were deemed as 'possibly' in four cases, and 'probably' in three cases to be related to the first azole antifungal as per the Naranjo criteria [6]. All had improvement in their LFT abnormalities after the switch to an alternative azole antifungal, however, in only two patients, did the LFTs normalise by the end of treatment (Case 3 and 4, Table 1). The most common concomitant medications include acetaminophen in all cases, penicillin/beta-lactamase inhibitors in 5 cases, antiemetics in 4 cases and chemotherapeutics in 3 cases (Table 1).

Voriconazole to fluconazole:

Of the three cases that switched from voriconazole to fluconazole, two were changed due to suspected drug-related toxicity and the third stepped down from treatment of possible invasive fungal infection to prophylaxis (Table 1). All had Grade 3 liver injury prior to the antifungal switch with peak GGT levels, from 518 to 735 IU/L (12.9 to 18.3 times the upper limit of normal (x ULN)) and two cases had elevated ALT levels of 140 to 186 IU/L (4.1 to 5.0 x ULN). Immediately prior to triazole antifungal switch, voriconazole levels were subtherapeutic in one patient (Case 1 0.34 mg/L one week prior) and within target range in two others (Case 2 1.48 mg/L three days prior; Case 3 2.87 mg/L five days prior). However, for Case 3, LFT abnormalities developed two weeks after a supratherapeutic level, when their voriconazole trough concentration was 5.94 mg/L. Notably, Case 3's LFT results did not improve with initial dose reduction. Although all three cases had improvement in their LFT results with the antifungal switch, one developed LFT abnormalities on day 50 coinciding with an episode of febrile neutropenia (Case 3). Case 2 was re-challenged with voriconazole 1 week later and had recurrence of their LFT abnormalities requiring a change in treatment to an alternative antifungal, micafungin.

Fluconazole to voriconazole:

The two children that switched from fluconazole to voriconazole did so for the treatment of a possible mold infection in the setting of febrile neutropenia (Table 1). One child (Case 4) was post-HSCT with concurrent GVHD (grade 1 skin and upper gastrointestinal disease). The GGT peaked 3 days after the switch to voriconazole (333 IU/L, 8.3 x ULN) and normalised by the end of the 55-day treatment course. Causality was assessed as 'possible' (Naranjo score 4) as the child was not subsequently rechallenged with fluconazole. The second child (Case 5, Table 1) was prescribed fluconazole after initial switch to voriconazole and the GGT derangement continued to improve despite this rechallenge. The case was also assessed as 'possible' (Naranjo score 2).

Voriconazole to itraconazole:

The child that was switched from voriconazole to itraconazole had supratherapeutic voriconazole concentrations 15 days prior (6.12 mg/L), with associated LFT abnormalities and rash (Case 6, Table 1). The dose was reduced by 16% however a repeat level was not taken. After the switch to itraconazole the LFTs normalised by day 34.

Posaconazole to fluconazole:

Posaconazole was switched to fluconazole in one case (Case 7, Table 1) in the setting of potential drug interactions with venetoclax during HSCT. This patients GGT peaked 10 days prior to the switch (137 IU/L, 2.8 x ULN) and remained elevated (113 IU/L) three days prior to switch but had improved within 11 days post switch (GGT 42 IU/L, 1.1 x ULN). However, the GGT began to uptrend reaching a peak of 290 IU/L 20 days post switch in the context of HSCT.

Discussion

This is the first pediatric case series to describe the outcome of switching triazole antifungal agents in the setting of AIH, highlighting this as a potential approach to managing drug-related hepatotoxicity. Given oral antifungal options in children are limited to triazole antifungals and AIH is the most common adverse event resulting in cessation of therapy [8], identifying an approach to managing AIH and preserving the use of this drug class is critical.

Published data on this approach to AIH are limited. Three case reports and one audit in adults demonstrated improvement after switching between triazole antifungals. Spellberg et al. described an adult with coccidioidal meningitis and fluconazole-related hepatotoxicity that improved with switching to voriconazole [2]. Further, a retrospective audit of 23 adults with acute myeloid leukemia who had switched from posaconazole to isavuconazole, demonstrated improvement in all 20 patients with CTCAE Grade 1 hepatotoxicity or more[1]. Of these, six patients had grade 3-4 abnormalities in liver transaminases with all patients showing improvement and in 2/6 patients, the LFTs normalised 4 weeks after the change in therapy[1]. A further case report described a patient with intracerebral aspergillosis who developed voriconazole-related hepatotoxicity which resolved after changing to posaconazole[3]. Similarly switching from voriconazole to posaconazole in combination with caspofungin was found to result in resolution of hepatotoxicity in an immunocompetent adult with invasive aspergillosis [4]. These data suggest a lack of cross-hepatotoxicity between triazole antifungals that requires further study.

The mechanism of liver injury from triazole antifungals is poorly understood but thought to be due to triazole alteration of inhibition of cytochrome P450 enzymes, acute inflammatory response, and mitochondrial dysfunction. An *in vivo* study in rats demonstrated worsening toxicity when fluconazole or itraconazole were administered a CYP450 inhibitor compared with azole therapy alone, suggesting CYP450 inhibition may have an important role in the mechanism of hepatotoxicity[9]. However, for posaconazole-induced hepatotoxicity, an *in vitro* study suggested a different mechanism, through mitochondrial dysfunction [10]. Data are limited on the relationship between azole dose and AIH for itraconazole and posaconazole, however, no clear relationship has been identified in pediatric studies of fluconazole and voriconazole [8, 11].

This case series adds to the growing body of evidence suggesting that there is a lack of cross-hepatotoxicity between azole antifungals and switching within the class is a potential approach to management of AIH. Further large clinical studies are needed to determine whether this approach could be routinely considered.

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Table I: Overview of patients with azole-induced hepatotoxicity whose liver functions tests improved after switching to another triazole antifungal

ID	Age, Sex	Underlying diagnosis	Antifungal 1 & dose prior to switch	Indication for antifungal therapy	Maximal LFT abnormalities; [?]ULN or patient's baseline	Maximal LFT abnormalities; [?]ULN or patient's baseline	CTCAE grade prior to switch [a]	Antifungal 2 & starting dose	Indication for switch	LFT results post switch; [?]ULN or patients' baseline	LFT results post switch; [?]ULN or patients' baseline	T t p r c r p s
Voriconazole switch to fluconazole	Voriconazole switch to fluconazole	Voriconazole switch to fluconazole	Voriconazole switch to fluconazole	Voriconazole switch to fluconazole	Voriconazole switch to fluconazole	Voriconazole switch to fluconazole	Voriconazole switch to fluconazole	Voriconazole switch to fluconazole	Voriconazole switch to fluconazole	Voriconazole switch to fluconazole	Voriconazole switch to fluconazole	Voriconazo s t f
1	4.2y M	Chronic granulomatous disease (HSCT)	Voriconazole 15.4mg/kg oral BD	Possible fungal infection	ALT GGT	x4.1 x18.3	2 3	Fluconazole 7.3mg/kg oral OD	Drug-related hepatotoxicity	ALT GGT	normalised normalised	F t a w
2	13.4y M	Acute myeloid leukemia (induction), acute appendicitis	Voriconazole 12.8mg/kg oral BD	Fungal prophylaxis	GGT	x12.9	3	Fluconazole 11.8mg/kg oral OD	None given	GGT	x7.2	F t a (w
3	7.5y M	Acute myeloid leukemia (HSCT)	Voriconazole 10.0mg/kg oral BD	Fungal prophylaxis	ALT GGT	x5.0 x15.5	2 3	Fluconazole 9.1mg/kg OD	Drug related hepatotoxicity	ALT GGT	x2.6 x1.1	F t a (w

ID	Age, Sex	Underlying diagnosis	Antifungal 1 & dose prior to switch	Indication for antifungal therapy	Maximal LFT abnormalities; [?]ULN or patient's baseline	Maximal LFT abnormalities; [?]ULN or patient's baseline	CTCAE grade prior to switch [a]	Antifungal 2 & starting dose	Indication for switch	LFT results post switch; [?]ULN or patients' baseline	LFT results post switch; [?]ULN or patients' baseline	T t p r c r p s
Fluconazole switch to voriconazole	Fluconazole switch to voriconazole	Fluconazole switch to voriconazole	Fluconazole switch to voriconazole	Fluconazole switch to voriconazole	Fluconazole switch to voriconazole	Fluconazole switch to voriconazole	Fluconazole switch to voriconazole	Fluconazole switch to voriconazole	Fluconazole switch to voriconazole	Fluconazole switch to voriconazole	Fluconazole switch to voriconazole	F s t v
4	16.6y F	Blastic plasmacytoid dendritic cell neoplasm (HSCT)	Fluconazole 4.7mg/kg oral OD	Fungal prophylaxis	GGT	x8.3	3	Voriconazole 2.3mg/kg oral BD	Febrile neutropenia - antifungal prophylaxis	GGT	normalised	F t a w
5	7.0y M	X-linked Hyper-IgM syndrome (HSCT)	Fluconazole 8.4mg/kg IV OD	Fungal prophylaxis	ALT GGT	x3.5 x6.8	2 3	Voriconazole 9.0mg/kg IV BD	Febrile neutropenia - treatment of possible infection	ALT GGT	x1.4 x3.6	F t a (w
Voriconazole switch to itraconazole	Voriconazole switch to itraconazole	Voriconazole switch to itraconazole	Voriconazole switch to itraconazole	Voriconazole switch to itraconazole	Voriconazole switch to itraconazole	Voriconazole switch to itraconazole	Voriconazole switch to itraconazole	Voriconazole switch to itraconazole	Voriconazole switch to itraconazole	Voriconazole switch to itraconazole	Voriconazole switch to itraconazole	V s t
6	5.7y M	T-cell acute lymphoblastic leukemia, febrile neutropenia	Voriconazole 7.5mg/kg oral BD	Fungal prophylaxis	GGT	x4.8	2	Itraconazole (2.5mg/kg oral twice a day)	Drug related hepatotoxicity	GGT	x3.0	1 w
Posaconazole switch to voriconazole	Posaconazole switch to voriconazole	Posaconazole switch to voriconazole	Posaconazole switch to voriconazole	Posaconazole switch to voriconazole	Posaconazole switch to voriconazole	Posaconazole switch to voriconazole	Posaconazole switch to voriconazole	Posaconazole switch to voriconazole	Posaconazole switch to voriconazole	Posaconazole switch to voriconazole	Posaconazole switch to voriconazole	P s t

ID	Age, Sex	Underlying diagnosis	Antifungal 1 & dose prior to switch	Indication for antifungal therapy	Maximal LFT abnormalities; [?]ULN or patient's baseline	Maximal LFT abnormalities; [?]ULN or patient's baseline	CTCAE grade prior to switch [a]	Antifungal 2 & starting dose	Indication for switch	LFT results post switch; [?]ULN or patients' baseline	LFT results post switch; [?]ULN or patients' baseline	T t p r c r p s
7	15.0y M	Acute myeloid leukemia relapse (HSCT)	Posaconazole MR 4.3mg/kg OD 5 days/week & 5.8mg/kg OD 2 days/week	Fungal prophylaxis	GGT	x2.8	2	Fluconazole 5.8mg/kg IV daily	Pre-HSCT, potential drug interactions	GGT	x1.1	1 w

References:

[a] CTCAE [5]: grade 2 (ALT grade 2 >3-5x ULN or patients baseline if baseline abnormal; ALT grade 3 >5-20; GGT grade 2 >2.5; GGT grade 3 >5-20x ULN).

[b] Naranjo score [6]: 1-4 possible association, score 5-8 probable association.

Abbreviations: LFT (Liver Function Test), CTCAE (Common Terminology Criteria for Adverse Events), ULN (Upper Limit of Normal), y (year), M (male), F (female), HSCT (Hematopoietic Stem Cell Transplant), ALT (Alanine Aminotransferase), GGT (Gamma Glutamyl Transferase), BD (Twice a Day), OD (Once a Day) MR (Modified Release)

Figure legends

Figure 1. Liver function tests before and after switching to another triazole antifungal agent. Panel A - Gamma-glutamyl transferase results; Panel B - Alanine aminotransferase results