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Observational cross-sectional case study of toxicities of antifungal drugs

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ABSTRACT

Objectives: In this study, we examined the toxicities, including poisoning and overdoses, with polyene, azole, flucytosine and echinocandin antifungals reported to the Swiss National Poison Centre.
Methods: An observational cross-sectional study on antifungals was performed based on reports between 1995 and 2016 to Tox Info Suisse. Patient demographic and clinical characteristics were summarised among all reported calls, stratified by age group. In secondary analyses, we evaluated cases with clinical follow-up information.
Results: In total, 149 cases were reported to the National Poison Centre during the study period, of which 49 (32.9%) were male and 91 (61.1%) were female, and 95 (63.8%) were adults and 54 (36.2%) were children (age ≤16 years). The most frequently reported drug class was azoles (136; 91.3%). In 31 cases (20.8%) reported by treating physicians, further clinical follow-up information was available. Nearly one-half of these patients were asymptomatic (15/31; 48.4%). In 11 patients (35.5%) among those with symptoms, the symptoms of toxicity were categorised with a strong causality to the respective antifungal. Clinical findings caused by triazoles were effects in the gastrointestinal tract, hallucinations and predelirium state. Clinical findings caused by polyenes were mostly minor symptoms with infusion-related effects or hypokalaemia. The severity was categorised as minor in 6 (54.5%) of 11 cases and as moderate in 5 cases (45.5%).
Conclusion: Despite high administered doses, no severe or fatal cases occurred within the study period. Although various toxicities can occur with antifungal administration and overdoses, they showed a favourable safety profile.

1. Introduction

Systemic antifungals are frequently used for the prevention or therapy of fungal infections [1]. Globally, over 1 billion individuals a year suffer from fungal infections [2]. The incidence of fungal infections has grown in recent decades owing to the increasing prevalence of immunocompromised patients, particularly those with cancer, AIDS (acquired immune deficiency syndrome), autoimmune disease and organ transplantation. Antifungals include diverse classes of medications that are approved for a broad variety of indications, ranging from nail infections and ringworm to fungal meningitis. Antifungals are used to treat invasive fungal infections among transplant recipients, cancer patients and immunodeficient patients. There are several classes of antifungals available, which are classified based on their chemical structure and mechanism of action. These include the polyenes (e.g. amphotericin B and its lipid formulations), azoles (e.g. triazoles and imidazoles), flucytosine and echinocandins (e.g. caspofungin).

As a group, antifungal medications for systemic use are relatively safe [3]. However, dose-dependent and drug-specific toxici-

Abbreviations: S.D., standard deviation; IQR, interquartile range.

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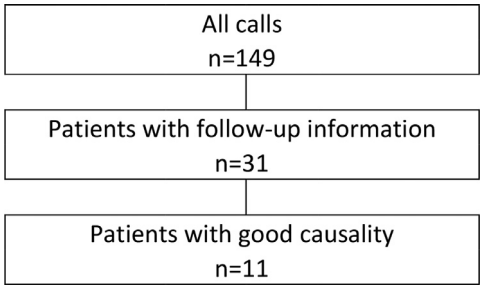

Figure 1. Flow chart with case selection.

ties can occur, ranging from mild or asymptomatic to potentially fatal reactions [4]. Common mild side effects include nausea, vomiting, fever, electrolyte disturbances, hallucinations and paranoia, dizziness and gastrointestinal symptoms [3,5]. While rare, severe adverse events include cardiac arrest, hypotension, QT prolongation, cardiac toxicity and hepatoxicity [6]. Acute liver injury is rare with polyene therapy, however, particularly with the lipid formulations, hepatocellular and cholestatic injury is a concern [7]. Additionally, infusion-related reactions, such as fever, chills and shaking, and nephrotoxicity have been reported with polyene therapy [8]. All azole antifungals are associated with an increased risk of liver injury [4]. The triazole fluconazole has become the most widely used azole partly due to its favourable safety profile, particularly compared with the imidazole ketoconazole [9]. In 2013, both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) concluded that the risk of fatal drug-induced liver injury associated with oral ketoconazole outweighed the benefits and it should no longer be prescribed [10].

However, despite a handful of observational studies, data regarding acute toxicity with antifungals are scarce and conflicting [11–16]. To our knowledge, no systematic analysis of data on antifungal toxicity from a national poisons centre has been published. Therefore, this observational cross-sectional study was performed with the aim to systematically evaluate the circumstances, symptoms, management and outcome of intoxications with antifungals.

Figure 1.

2. Materials and methods

2.1. Poisons centre operational procedures and data management

The Swiss National Poisons Information Centre offers complimentary, nationwide consulting regarding intoxications for physicians and the general population. Any individual in Switzerland can call the 24-h service for suspected overdose or poisoning. The service is open to members of the public, doctors and other health professionals. At the time of the call, basic demographic and clinical data are gathered systematically and standardised by a clinical toxicologist. Routinely collected information include the age of the patient, sex, weight, circumstances of exposure, drug, route of administration and other drugs received. Additionally, follow-up reports may be completed by the treating physicians. These additional data contain further information regarding the underlying conditions, dose of involved substances, clinical findings, symptoms, decontamination measures and clinical course. For each case, a standardised causality and severity assessment is performed by an experienced clinical toxicologist. The severity of the symptoms is categorised into ‘mild’, ‘moderate’ and ‘severe’ according to the poisoning severity score [17]. Extraordinary cases are rated independently by a second clinical toxicologist or are discussed in an expert group. Each case record is checked for integrity and validity by a clinical toxicologist before the case is integrated in the database. The National Poisons Information Centre is primarily contacted in cases of acute exposures to toxins. Therefore, chronic exposures after long-term use or prolonged toxicities and extended effects such as carcinogenesis are not available in this data set of acute situations from poisons information centres. Moreover, in acute poisoning, various factors such as the duration of treatment or specific patient characteristics are of subordinate importance. Therefore, they are not routinely collected.

2.2. Study design

An observational cross-sectional study was conducted where all cases of overdoses and reactions with antifungals reported to the Swiss National Poisons Information Centre between 1 January 1995 and 31 December 2016 were included. No exclusion criteria were applied.

2.3. Data analysis

A descriptive analysis of all reports was performed. Demographic characteristics were reported overall and stratified by age grouping [adult or child (age $\leq$16 years) at the time of the call]. For variables with normally distributed values, the mean $\pm$ standard deviation or counts with proportions were calculated, as appropriate. In a secondary analysis, only cases reported by treating physicians with additional clinical follow-up information were included. Finally, among the cases with follow-up information, we summarised the clinical symptoms and underlying conditions in patients with sufficient causality (probable and certain in overdoses, including possible in adverse reactions). Additionally, where possible, the dose was related to the recommended dose to assess a relationship between dose and symptom severity. Ethics Committee approval was granted by the Zurich Cantonal Ethics Review Board according to Swiss law.

3. Results

Annual calls related to pharmaceuticals ranged between 6430 to 11 251 (41% to 35% of all calls) in the years 1995 to 2016; 0.07% of all calls related to pharmaceuticals were in association with an antifungal. The data included 149 initial calls, of which approximately two-thirds were among adults (n = 95) and one-third were for children (n = 54) (Table 1). The mean age of all cases was 21.2 $\pm$ 25.2 years and was 47.3 $\pm$ 19.4 years and 3.1 $\pm$ 3.2 years in adults and children, respectively. There was a higher proportion of missing age data among adults (62.1%) compared with children (3.7%). Overall, the majority of cases were female (n = 91; 61.1%). However, this differed between adults and children; 72.6% of adults but only 40.7% of children were female (Table 1).

The most common drugs were azoles, which were reported in 87.4% (n = 83) of adult exposures and 98.1% (n = 53) of child exposures. According to the date of commercialisation in Switzerland, 2 cases (1.3%) were reported with miconazole (date 1972), 8 cases (5.4%) with ketoconazole (1981), 79 cases (53.0%) with fluconazole (1989), 43 cases (28.9%) with itraconazole (1992), 8 cases (5.4%) with voriconazole (2002) and none related to posaconazole (2007). Over 85% of exposures reported that the main route of administration was oral. The most frequently reported circumstances of poisoning were acute situations circumstances (n = 89; 59.7%), particularly among children where 96.3% (n = 52) of poisonings fell in the category. The majority (n = 127; 85.2%) of calls reported the antifungal medication as the only ingested medication (monointoxication) both for adults (n = 85; 89.5%) and children (n = 42; 77.8%). The most common concomitant drugs were pain and cold medications. A complete list of all reported co-medications can be found in Supplementary Table S1.

Table 1
Demographic characteristics of all calls reported to the National Poison Center, stratified by calls related to adults and children

Characteristic	All calls (N = 149)	Adults (>16 years) (N = 95)	Children (≤16 years) (N = 54)
Age (years)			
Mean ± S.D.	21.2 ± 25.2	47.3 ± 19.4	3.1 ± 3.2
Median (IQR)	4.8 (2.0–36.5)	47.0 (30.0–60.3)	2.0 (1.0–4.0)
Unknown age [n (%)]	61 (40.9)	59 (62.1)	2 (3.7)
Sex [n (%)]			
Male	49 (32.9)	24 (25.3)	25 (46.3)
Female	91 (61.1)	69 (72.6)	22 (40.7)
Unknown	9 (6.0)	2 (2.1)	7 (13.0)
Antifungal drug [n (%)] [a]			
Polyenes	7 (4.7)	6 (6.3)	1 (1.9)
Azoles	136 (91.3)	83 (87.4)	53 (98.1)
Echinocandins	1 (0.7)	1 (1.1)	–
Flucytosine	–	–	–
Combination	5 (3.4)	5 (5.3)	–
Route of administration [n (%)]			
Oral	130 (87.3)	82 (86.3)	48 (88.9)
Vaginal	6 (4.0)	3 (3.2)	3 (5.6)
Intravenous	9 (6.0)	6 (6.3)	3 (5.6)
Paravenous	2 (1.3)	2 (2.1)	–
Ocular	1 (0.7)	1 (1.1)	–
Unknown	1 (0.7)	1 (1.1)	–
Circumstance of overdose [n (%)]			
Suicidal	9 (6.0)	8 (8.4)	1 (1.9)
Acute	89 (59.7)	37 (38.9)	52 (96.3)
Intentional	8 (5.4)	4 (4.2)	4 (7.4)
Unintentional	81 (54.4)	33 (34.7)	48 (88.9)
Chronic	19 (12.8)	18 (18.9)	1 (1.9)
Intentional	7 (4.7)	6 (6.3)	1 (1.9)
Unintentional	12 (8.1)	12 (12.6)	–
Adverse drug reaction	32 (21.5)	32 (33.7)	–
Type of overdose [n (%)]			
Monointoxication	127 (85.2)	85 (89.5)	42 (77.8)
Polyintoxication [a]	22 (14.8)	10 (10.5)	12 (22.2)
Other antifungal	4 (2.7)	2 (2.1)	2 (3.7)
Neuroleptics	2 (1.3)	–	2 (3.7)
Antihistamine	1 (0.7)	1 (1.1)	–
Cold medication	5 (3.4)	4 (4.2)	1 (1.9)
Antibiotics	4 (2.7)	–	4 (7.4)
Benzodiazepines	1 (0.7)	1 (1.1)	–
Local anaesthetic	2 (1.3)	2 (2.1)	–
Muscle relaxant	2 (1.3	2 (2.1)	–
Pain medication	5 (3.4)	3 (3.2)	2 (3.7)
Antilipaemics	2 (1.3)	1 (1.1)	1 (1.9)
Other (non medicinal)	3 (2.0)	2 (2.1)	1 (1.9)

S.D., standard deviation; IQR interquartile range.
[a] Not mutually exclusive as patients may report more than one medication.

Similar results were seen for the 31 cases with follow-up information reported by treating physicians (Table 2). From these 31 cases, 18 (58.1%) were adults and 13 (41.9%) were children. The mean age was 27.9 ± 27.2 years overall and was 48.2 ± 19.8 years in adults and 2.9 ± 2.6 years in children. Similar to all calls, the distribution of sex differed between adults and children, with a higher proportion of females (n = 14; 77.8%) among adults compared with children (n = 5; 38.5%). The most frequent antifungal drug class was azoles, and the most frequent route of administration was oral in all groups. Of the 23 cases related to azole antifungals, 1 case was reported with ketoconazole, 10 cases with fluconazole, 8 cases with itraconazole and 4 with voriconazole. Overall, acute poisonings were the most commonly reported (n = 18; 58.1%), particularly among children (n = 12; 92.3%). The majority of calls were reported without symptoms (n = 15; 48.4%). However, among adults >60% of calls reported mild (27.8%) or moderate (33.3%) symptoms.

We further stratified by causality investigating the clinical symptoms and underlying conditions of patients with strong causality (Table 3). In the 11 patients with a strong causality, the majority were adults (n = 9; 81.8%), female (n = 9; 81.8%) and taking azoles (n = 9; 81.8%). One female paediatric patient (age 9 years) with acute myeloid leukaemia received a dose of 0.52 mg/kg amphotericin B intravenously and developed tachycardia, shivering and rise in temperature (40.7°C) 30 min after administration. Hypokalaemia with a potassium level of 2.9 mmol/L was also reported. Another paediatric patient (age 3 years) experienced mild symptoms with diarrhoea, abdominal pain and lethargy following oral itraconazole. Among the two cases with polyenes (both with amphotericin deoxycholate), one suffered cardiovascular problems with tachycardia and hypokalaemia and a fever >40°C with significant chills, while the other had skin reactions, including erythema, pruritus and pain. Among intoxications with azoles (one with ketoconazole, three with fluconazole, three with itraconazole and two with voriconazole), minor clinical symptoms included nausea (itraconazole) and diarrhoea (voriconazole), dizziness, hallucinations (fluconazole) and fatigue (itraconazole), and skin reactions (paraesthesia and redness) (ketoconazole). Only the azoles (itraconazole, fluconazole and voriconazole) were associated with adverse effects of the liver, pancreas or gall bladder, including increased transaminases, cholecystolithiasis, cholecystitis, cholestatic hepatitis, hepatocellular necrosis and oedematous pancreatitis (Table 3).

Table 2
Demographic characteristics of patients reported by treating physician to the National Poison Centre, stratified by calls related to adults and children

Characteristic	All patients (N = 31)	Adults (>16 years) (N = 18)	Children (≤16 years) (N = 13)
Age (years)			
Mean ± S.D.	27.9 ± 27.2	48.2 ± 19.8	2.9 ± 2.6
Median (IQR)	27.0 (3.1–52.0)	49.0 (35.0–58.0)	2.0 (1.5–4.0)
Sex [n (%)]			
Male	11 (35.5)	4 (22.2)	7 (53.9)
Female	19 (61.3)	14 (77.8)	5 (38.5)
Unknown	1 (3.2)	–	1 (7.7)
Antifungal drug [n (%)] [a]			
Polyenes	4 (12.9)	3 (16.7)	1 (7.7)
Azoles	23 (74.2)	11 (61.1)	12 (92.3)
Echinocandins	1 (3.2)	1 (5.6)	–
Flucytosine	–	–	–
Combination	3 (9.7)	3 (16.7)	–
Route of administration [n (%)]			
Oral	23 (74.2)	12 (66.7)	11 (84.6)
Intravenous	6 (19.4)	4 (22.2)	2 (15.4)
Paravenous	2 (6.5)	2 (11.1)	–
Circumstance of overdose [n (%)]			
Suicidal	2 (6.5)	2 (11.1)	–
Acute	18 (58.1)	6 (33.3)	12 (92.3)
Intentional	1 (3.2)	–	1 (7.7)
Unintentional	17 (54.8)	6 (33.3)	11 (84.6)
Chronic	6 (19.3)	5 (27.8)	1 (7.7)
Intentional	1 (3.2)	–	1 (7.7)
Unintentional	5 (16.1)	5 (27.8)	–
Adverse drug reaction	3 (9.7)	3 (16.7)	–
Iatrogenic	2 (6.5)	2 (11.1)	–
Type of overdose [n (%)]			
Monointoxication	26 (83.9)	13 (72.2)	13 (100.0)
Polyintoxication [b]	5 (16.1)	5 (27.8)	–
Symptoms [n (%)]			
No symptoms	15 (48.4)	6 (33.3)	9 (69.2)
Mild	7 (22.6)	5 (27.8)	2 (15.4)
Moderate	7 (22.6)	6 (33.3)	1 (7.7)
Severe	–	–	–
Fatal	–	–	–
Not classified	2 (6.5)	1 (5.6)	1 (7.7)
Causality [n (%)]			
Certain	1 (3.2)	1 (5.6)	–
Probable	8 (25.8)	6 (33.3)	2 (15.4)
Possible	2 (6.5)	2 (11.1)	–
Unlikely	3 (9.7)	2 (11.1)	1 (7.7)
Unclassified	17 (54.8)	7 (38.9)	10 (76.9)

S.D., standard deviation; IQR, interquartile range.
[a] Not mutually exclusive as patients may report more than one medication.

No cardiovascular adverse effects were associated with the azoles.

Dose information was only available in a minority of patients thus limiting the interpretation of dose–toxicity relationships. In one patient with a dose of fluconazole 10.5 times higher than recommended (400 mg oral) hallucinations occurred (individual patient data not shown). Another patient with a 4 times higher dose of fluconazole intoxication experienced hallucinations. One patient with a 4.3 times higher dose of voriconazole (recommended 6 mg/kg) experienced moderate symptoms of the central nervous system and the liver. Following a 1.8 times increased dose (recommended 6 mg/kg) of voriconazole one patient suffered from minor hepatic symptoms (data not shown).

4. Discussion

In this study of the Swiss National Poisons Information Centre, toxicities observed were generally mild to moderate, and no severe or fatal cases were reported. Among a subset of reports with medical follow-up information, the reported effects ranged from mild clinical symptoms to hepatocellular necrosis. Among the moderate adverse events, polyenes were associated with cardiovascular events, while azoles were associated with hepatoxicity. No severe events were observed among reports of flucytosine or echinocandins.

4.1. Limited data on poisoning

Data on antifungal toxicities are rare. The rarity of published data may either reflect an underestimation of the problem or the lack of serious events. The present study aimed to fill this knowledge gap. Our results are generally in line with the available literature on the safety of polyenes and azoles. While the most significant adverse effect with polyenes is renal toxicity, we identified only one patient with increased plasma creatinine [8,18]. Renal toxicity resulting from amphotericin poisoning, which is often a reversible and transient effect of amphotericin treatment [19–22], was not reported in our cases. Additionally, recently published medication errors by confusing amphotericin B preparations [23,24] were not observed. Within our study sample of patients reported by clinicians and with additional clinical information, only a single patient reported elevated creatinine levels. Overall, the majority of reported symptoms with polyenes were minor, including

Table 3
Clinical characteristics [*n* (%)] among cases with follow-up information with strong causality assessment[a]

Characteristic	All calls ($N = 11$)	Polyenes ($N = 2$)	Azoles ($N = 9$)
Adults	9 (81.8)	1 (50.0)	8 (88.9)
Children	2 (18.2)	1 (50.0)	1 (11.1)
Sex			
Male	1 (9.1)	–	1 (11.1)
Female	9 (81.8)	2 (100.0)	7 (77.8)
Unknown	1 (9.1)	–	1 (11.1)
Antifungal drug			
Polyenes	2 (18.2)	2 (100.0)	–
Azoles	9 (81.8)	–	9 (100.0)
Route of administration			
Oral	8 (72.7)	–	8 (88.9)
Intravenous	2 (18.2)	1 (50.0)	1 (11.1)
Paravenous	1 (9.1)	1 (50.0)	–
Circumstance of overdose			
Suicidal	1 (9.1)	–	1 (11.1)
Acute	4 (36.3)	2 (100.0)	2 (22.2)
Intentional	1 (9.1)	–	1 (11.1)
Unintentional	3 (27.3)	2 (100.0)	1 (11.1)
Chronic	1 (9.1)	–	1 (11.1)
Intentional	1 (9.1)	–	1 (11.1)
Unintentional	–	–	–
Adverse drug reaction	3 (27.3)	–	3 (33.3)
Iatrogenic	2 (18.2)	–	2 (22.2)
Type of overdose			
Monointoxication	9 (81.8)	2 (100.0)	7 (77.8)
Polyintoxication	2 (18.2)	–	2 (22.2)
Clinical symptoms [b]			
Fatigue/tiredness	1 (9.1)	–	1 (11.1)
Fever	1 (9.1)	1 (50.0)	–
Chills	1 (9.1)	1 (50.0)	–
Nausea	1 (9.1)	–	1 (11.1)
Diarrhoea	1 (9.1)	–	1 (11.1)
Dizziness/confusion	2 (18.2)	–	2 (22.2)
Hallucination	1 (9.1)	–	1 (11.1)
Skin reaction [c]	3 (27.3)	1 (50.0)	2 (22.2)
Cholestatic hepatitis	1 (9.1)	–	1 (11.1)
Cholecystitis	1 (9.1)	–	1 (11.1)
Hypokalaemia	1 (9.1)	1 (50.0)	–
Hepatocellular necrosis	2 (18.2)	–	2 (22.2)
Elevated transaminase	3 (27.3)	–	3 (33.3)
Oedematous pancreatitis	1 (9.1)	–	1 (11.1)
Tachycardia	1 (9.1)	1 (50.0)	–
Severity			
Minor	6 (54.5)	1 (50.0)	5 (55.6)
Moderate	5 (45.5)	1 (50.0)	4 (44.4)
Severe	–	–	–
Fatal	–	–	–
Underlying condition			
Acute myeloid leukaemia	1 (9.1)	1 (50.0)	–
Eye fungus	2 (18.2)	–	2 (22.2)
Cryptococcus	1 (9.1)	–	1 (11.1)
Other	3 (27.3)	–	3 (33.3)
Unknown	4 (36.4)	1 (50.0)	3 (33.3)

[a] Strong causality include reports with causality assessed as 'probable/certain/likely'.
[b] Not mutually exclusive categories; patients may present with more than one clinical symptom.
[c] Skin reactions included erythema, pruritus, skin pain, skin redness and paraesthesia.

dizziness, fever, chills and nausea, which are common infusion-related reactions of parenterally administered polyenes.

In our study, intoxications were mainly observed with the azoles, which are a broadly administered antifungal class with oral availability. Among these, the most frequently reported azoles were fluconazole, followed by itraconazole. Similar to reports with polyenes, the majority of clinical symptoms reported among patients with physician-reported clinical information were mild with all azoles. In one case we observed cholestatic hepatitis associated with itraconazole administration, which is in line with a previous case report [25]. Similar to a previous large observational study, cases of acute liver injury appeared to be low in our analysis and we did not identify a higher reporting of liver toxicity between azoles [26]. Three patients exhibited mild transaminase increases following the use of azoles, of which two patients reported hepatocellular necrosis. Finally, while both fluconazole and voriconazole can lead to QT prolongation, leading to Torsades de pointes, we did not identify any reports of cardiac arrythmias or cardiac death in our data.

In our analysis, we observed five cases with combinations of antifungals [27], three of which included additional clinical information. In two of the three cases flucytosine and amphotericin B were reported, while in one a combination of triazoles were ingested. These few cases do not support an increased risk or ag-

gravated effects with combinations. However, general recommendations on the choice of treatment or dosage cannot be provided based on the number and severity of toxicities from this study. In our study, no patients' reactions were graded as severe or had a fatal outcome. Quantitative toxicities of antifungals with thresholds for (severe) symptoms and adverse effects remain not well defined for antifungal classes or antifungal substances. As calls to poisons information centres also reflect the market penetration of the products, cases with new antifungals such as posaconazole were not observed within this study period.

When interpreting our results, we are mindful of the limitations inherent to our data. We were hindered by missing or incomplete data. In particular, there was a high proportion of missing information on the administered dose, which hampered the assessment of the dose–effect relationship, i.e. calculation of the association between the dose and severity. Moreover, duplicates of calls for a specific subject might have occurred. Acute intoxications and reactions are commonly emergency situations, where the initial call is focused on the most important and potentially life-saving factors. Moreover, data from poisons centres may be subject to reporting bias [28]. Therefore, it is plausible that chronic or delayed toxicities were not observed (or were underreported) in our study. Data on discontinuation of therapies owing to antifungal toxicities and dose adjustments with regard to adverse events were not available in the data. However, the decision to continue a treatment against systemic fungal infections is based on the severity of the disease and the seriousness of the toxicity. Therefore, this risk–benefit assessment should be based on an individual therapeutic decision such as the indication of the antifungal and the severity of the toxicity. Additionally, the small number of patients with clinical follow-up information limited our ability to assess the individual antifungal classes, and these results should therefore be interpreted with caution. Methods of data collection, including route of contact, selection of cases and urgency of the situation differ from pharmacovigilance studies. Therefore, further suspected toxicities or delayed effects might be better reflected in other types of studies.

In conclusion, intoxications with antifungal drugs were mainly reported with oral azoles, while the majority of patients remained asymptomatic. Toxicities of antifungal drugs were generally mild to moderate, with no severe or fatal outcomes reported to the National Poison Centre during the study period. Importantly, while high documented doses were reported, they were not associated with severe adverse events. Thus, the evidence from our data is in line with other clinical studies suggesting that antifungals, in particular azoles, are well tolerated with a broad therapeutic margin.

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None.

Competing interests

SW is a member of the Human Medicines Expert Committee (HMEC) of Swissmedic and an expert for the European Medicines Agency. The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of an agency or one of the committees or working parties. All other authors declare no competing interests.

Ethical approval

Ethical approval was granted by the Zurich Cantonal Ethics Review Board [No. 2014-0467] according to Swiss law.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jgar.2021.11.010.

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