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Risk of serious skin disorders among users of oral antifungals: a population-based study

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Abstract

Background: Serious skin disorders have been associated with the use of oral antifungals in a number of case reports and series of cases. However the incidence of these disorders remains unknown.

Methods: We estimated the risk of serious skin disorders in a cohort of users of oral antifungals identified in the general population of the General Practice Research Database in the UK. The cohort included 61,858 patients, 20 to 79 years old, who had received at least one prescription for either oral fluconazole, griseofulvin, itraconazole, ketoconazole, or terbinafine.

Results: The background rate of serious cutaneous adverse reactions (the one corresponding to non use of oral antifungals) was 3.9 per 10,000 person-years (95% CI 2.9–5.2). Incidence rates for current use were 15.4 per 10,000 person-years (1.9–55.7) for itraconazole, 11.1 (3.0–28.5) for terbinafine, 10.4 (1.3–37.5) for fluconazole, and 4.6 (0.1–25.8) for griseofulvin. Itraconazole was the antifungal associated with the highest relative risk, 3.9 (0.5–15.0), when compared to the risk among non users, followed by terbinafine and fluconazole, with relative risks of 2.8 (0.7–7.8) and 2.6 (0.3–10.1), respectively.

Conclusions: We conclude that cutaneous disorders associated with the use of oral antifungals in this study were all of mild severity and that the risk associated with the use of oral antifungals was slightly higher than the risk in non-users. The safety profile of terbinafine regarding cutaneous disorders is similar to other antifungals and in the very low range of risks associated with other drugs.

Background

Serious skin disorders including toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, angioedema and acute generalized exanthematous pustulosis have been associated with the use of oral antifungals in a number of case reports and retrospective series of cases. However, studies examining the risk associated with the use of oral antifungal drugs are not available.

Table 1: OXMIS codes used for case identification

OXMIS code	Diagnosis
6951	Erythema multiforme
6951	Erythema multiforme exudativum
6951	Syndrome Stevens-Johnson
6951	Necrolysis toxic epidermal
L7090	Lyell's disease
L7090	Epidermal necrolysis
6869	Eczema pustular
7882	Rash pustular
7080	Angioneurotic oedema
7080	Angio-oedema
7080	Oedema Quincke's
7080	Oedema supraglotic allergic
6959	Dermatitis exfoliative
9779	Eruption skin due drug ingested

In the present study we estimated the risk of potentially serious skin disorders in a cohort of users of oral antifungals identified in the general population of UK using the General Practice Research Database (GPRD).

Population and methods

Source population

The GPRD contains clinical computerized information entered in a standardized manner by general practitioners (GPs) on their patients. Around 1,500 GPs, covering a population exceeding 3 million, have agreed to provide systematically their data files anonymously to the Office of National Statistics (ONS) and to allow the information to be used for research purposes.[1] Upon receiving the data from the GPs, ONS organizes this information and performs a series of quality checks. The computerized information includes demographics, details of each visit, a summary of specialists' clinical notes and hospital letters, results of laboratory tests and a free text section. A modification of the Oxford Medical Information System (OXMIS) classification system is used to code specific diagnoses, and a drug dictionary based on data from the Prescription Pricing Authority is used to code drugs.[2] Prescriptions issued by the general practitioner are directly generated by the computer system with dosage instructions included. Also, the indication for treatment is required for all new courses of therapy. Recorded information can be validated and completed through review of original paper-based medical records. Validation studies with the GPRD have documented the recording of medical data in the GP's computers to be near to complete.[3,4]

Study cohort

The study cohort comprised all patients aged 20–79 who had received at least one prescription for either oral fluconazole, griseofulvin, itraconazole, ketoconazole, or terbinafine between January 1, 1991 and March 31, 1997. We excluded all patients with a prior history of diseases or conditions predisposing to cutaneous disorders including neoplasms, AIDS, and systemic and immunosupressive disorders and therapies. Patients with a previous history of skin disorders were similarly excluded. The final study cohort was constituted by 61,858 patients. We followed-up each patient in the study cohort from the date of the first antifungal drug prescription until the earliest occurrence of: a) code for any of the study endpoints: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, angioedema, or acute generalized exanthematous pustulosis; b) one of the exclusion conditions mentioned above; c) age greater than 80; d) death; or e) date of end of the study period.

Case definition and ascertainment

In a first step we identified potential cases through an automated search for the OXMIS codes listed in table 1. The computerized information of these potential cases was manually reviewed to discard patients with any of the study exclusion criteria: neoplasms, AIDS, and systemic and immunosupressive disorders and therapies. The remaining cases were validated through a structured questionnaire administered to the GPs along with review of all medical records provided anonymously by the GPs. All the process of case identification and validation was done blindly to the use of medications.

We defined as a case of potentially serious skin disorder any patient in the study cohort with a first ever diagnosis of toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, angioedema, or acute generalized exanthematous pustulosis, recorded in the database during the study period. We required confirmation of the diagnosis based on the questionnaire filled by the GP and the review of medical records when available.

Exposure definition

Person time at risk was aggregated in three different time windows according to use of the study antifungal drugs. Current use encompassed all the days of prescribed treatment plus an additional period of 14 days at the end of treatment. Past use was defined as the period of 90 days following the time window of current use. Finally, the time period starting after past use was defined as non use.

Analysis

Incidence rates of serious skin disorders were calculated using as denominator both the number of patients exposed to each individual antifungal drug and the corre-

Table 2: Age and sex distribution of the study cohort of users of oral antifungals*

	Fluconazole		Griseofulvin		Itraconazole		Ketoconazole		Terbinafine	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Sex										
Women	24,236	(90)	2,003	(41)	11,474	(75)	394	(53)	6,017	(43)
Men	2,756	(10)	2,938	(59)	3,855	(25)	343	(47)	7,842	(57)
Age										
20–39	13,742	(51)	1,585	(32)	7,678	(50)	334	(45)	3,927	(28)
40–59	10,340	(38)	2,210	(45)	5,848	(38)	267	(36)	6,281	(45)
60–69	1,767	(7)	737	(15)	1,150	(8)	91	(12)	2,338	(17)
70–79	1,143	(4)	409	(8)	653	(4)	45	(6)	1,313	(9)
Total	26,992		4,491		15,329		737		13,859	

* Some of the cohort members received more than one antifungal drug during the study period.

Table 3: Exclusions after review of computer patient profiles and medical records

Diagnosis not confirmed	6
Other skin disorders	36
Rash	23
Focalized eczema	7
Acne	1
Erysipela	1
Pityriasis rosacea	1
Lichen planus	1
Candidiasis	1
Benign dermatofibroma	1
Prior history	4
Exclusion criteria*	2
Medical record not available	3
Total excluded	51

*One patient had a bronchogenic carcinoma and the other was HIV positive

sponding person-time at risk. Ninety-five percent confidence intervals were computed on the basis of a Poisson distribution of case counts within categories of use.[5] The Stata program was used to obtain estimates of rate ratios.[6]

Results

A total of 61,858 patients received 120,807 prescriptions for oral antifungals. The age and sex distribution of the study cohort is presented in table 2. Fluconazole, itraconazole, and ketoconazole were mainly prescribed to young women, whereas griseofulvin and terbinafine were predominantly prescribed to middle aged men.

We identified 113 potential cases of serious skin disorders. Of these, 26 (23%) were excluded after review of their computerized information. Medical records were requested to the GPs for the remaining 87 patients. Review of medical records led to confirm 62 cases and to exclude 25 additional patients. For three of these excluded patients medical records were not available. The reasons of exclusion after the review of both computerized information and medical records are summarized in table 3.

Of the 62 confirmed cases, 47 (76%) occurred during the period of non use of oral antifungals, 6 (10%) during past use, and 9 (14%) during current use. Specific diagnostics for the three categories of use are presented in table 4. Angioedema was the more frequent disorder (65%), followed by erythema multiforme (21%). There were two cases of Stevens-Johnson syndrome and one case of dermatitis exfoliative. No cases of toxic epidermal necrolysis and acute generalized exanthematous pustulosis were identified. None of the 62 cases was life-threatening. Most cases (69%) were diagnosed and managed by the GP, 17 cases (27%) by the dermatologist, and two (3%) required hospitalization. These two cases with hospitalization occurred among non-users of oral antifungals.

Rates in non-users

The overall background rate corresponding to non-users of oral antifungals was 3.9 per 10,000 person-years (95% CI 2.9–5.2). Among non-users there were 32 (68%) cases with angioedema, 13 (28%) with erythema multiforme, 1 (2%) with dermatitis exfoliative, and 1 (2%) Stevens-Johnson syndrome. Most cases (68%) were diagnosed

Table 4: Serious skin disorders according to source of diagnosis

Source of diagnosis	Diagnosis	Current use	Past use	Non use	Overall
General practitioner	Angioedema	3	2	24	29
	Erythema multiforme	3	2	6	11
	Stevens-Johnson syndrome	1	0	1	2
	Dermatitis exfoliative	0	0	1	1
Dermatologist	Angioedema	2	1	6	9
	Erythema multiforme	0	1	7	8
Hospitalization	Angioedema	0	0	2	2
Total		9	6	47	62

Table 5: Characteristics of cases of serious skin disorders with current exposure to oral antifungals

Current use	Age	Sex	Duration of treatment (days)	Dose (mg)	Diagnosis	Source of diagnosis	Co-medication potentially related with serious skin disorders
Fluconazole	45	F	18	50	Angioedema	Dermatologist	None
Fluconazole	20	F	1	150	Erythema multiforme	GP	None
Griseofulvin	55	M	50	500	Angioedema	GP	Cefalexine, diclofenac
Itraconazole	35	F	58	100	Angioedema	Dermatologist	Prednisolone
Itraconazole	63	M	6	100	Erythema multiforme	GP	None
Terbinafine	64	M	172	250	Angioedema	Dermatologist	None
Terbinafine	35	F	75	250	Angioedema	GP	None
Terbinafine	56	M	26	250	Stevens-Johnson syndrome	GP	None
Terbinafine	27	F	6	250	Erythema multiforme	GP	None

M = Male; F = Female;GP = General Practitioner

and managed by the general practitioner, 13 (28%) by the dermatologist and 2 (4%) required hospitalization. These two last cases were hospitalized because of angioedema. The two cases of dermatitis exfoliative and Stevens-Johnson syndrome were both diagnosed by the general practitioner.

Rates in current users

For current users, two cases occurred during treatment with fluconazole (one angioedema and one erythema multiforme), one with griseofulvin (angioedema), two with itraconazole (one angioedema and one erythema multiforme) and four with terbinafine (two cases with angioedema, one with erythema multiforme, and one with Stevens-Johnson syndrome) (table 5). The case with Stevens-Johnson syndrome was diagnosed and managed by the general practitioner without requiring hospitalization. Concurrent treatment with drugs potentially related with serious skin disorders was found in two patients, both with angioedema. One exposed to griseofulvine was taking cefalexine and diclofenac and the other with current use of itraconazole was concurrently treated with prednisolone.

Incidence rates of serious cutaneous disorders for current use of individual antifungal drugs are presented in table 6. The highest rate was for itraconazole (15.4 per 10,000 person-years), followed by terbinafine (11.1 per 10,000 person-years), fluconazole (10.4 per 10,000 person-years), and griseofulvin (4.6 per 10,000 person-years). Itraconazole was the antifungal drug associated with the greatest relative risk (3.9, 95% CI 0.5–15.0) compared to the background risk of non users, followed by terbinafine (2.8, 95% CI 0.7–7.8) and fluconazole (2.6, 95% CI 0.3–10.1).

Table 6: Crude incidence rates of serious skin disorders among current users of oral antifungals

Antifungal	Patients	Person-years	Cases	Cumulative incidence per 10,000 patients	Incidence rate per 10,000 person-years	Relative risk* (95% CI)
Fluconazole	26,992	1,927	2	0.7 (0.01–2.7)	10.4 (1.3–37.5)	2.6 (0.3–10.1)
Griseofulvin	4,941	2,158	1	2.0 (0.1–11.3)	4.6 (0.1–25.8)	1.2 (0.03–6.9)
Itraconazole	15,329	1,296	2	1.3 (0.2–4.7)	15.4 (1.9–55.7)	3.9 (0.5–15.0)
Ketoconazole	737	89	0	0.0 (0.0–50.1)	0.0 (0.0–414.3)	0.0 (0.0–109.9)
Terbinafine	13,859	3,596	4	2.9 (0.8–7.4)	11.1 (3.0–28.5)	2.8 (0.7–7.8)

CI = Confidence interval * Incidence rate ratio using non-use person-time as the reference category.

Table 7: Characteristics of cases of serious skin disorders with past exposure to oral antifungals

Past use	Age	Sex	Duration of treatment (days)	Days from last dose intake to initial symptoms	Dose (mg)	Diagnosis	Source of diagnosis	Current use with drugs potentially related with serious skin disorders
Fluconazole	57	F	1	43	150	Erythema multiforme	Dermatologist	Cefaclor
Fluconazole	37	F	1	55	150	Angioedema	GP	None
Terbinafine	76	M	196	16	250	Angioedema	Dermatologist	Claritromicine
Terbinafine	46	F	28	63	250	Angioedema	GP	None
Terbinafine	47	F	28	77	250	Erythema multiforme	GP	Flucoxacilline
Terbinafine	48	M	14	28	250	Erythema multiforme	GP	None

M = Male; F = Female;GP = General Practitioner

Rates in past users

Of the six cases with past use of oral antifungals four had been exposed to terbinafine (two with angioedema and two with erythema multiforme) and two to fluconazole (one angioedema and one erythema multiforme) (table 7). The number of days from the end of treatment with oral antifungals to start of symptoms ranged from 16 to 77 for past users of terbinafine. The number of days were 43 and 55 for the two past users of fluconazole. Current use of other drugs potentially related with serious skin disorders was found in two patients with past exposure to terbinafine and in one patient with past use of fluconazole. The incidence rate of serious skin disorders for past users of terbinafine was 11.1 per 10,000 person-years (95% CI 3.0–28.3) and that for past users of fluconazole 2.1 (0.3–7.7). The corresponding relative risk compared to the rate in non-users were 2.8 (1.0–7.8) for terbinafine and 0.5 (0.1–2.2) for fluconazole (table 7).

Discussion

In this study we estimated the risk of serious skin disorders in a cohorts of 61,858 users of oral antifungals. Of the 62 confirmed cases 9 occurred among current users, 6 among past users, and 47 among non-users of oral antifungals. The risk associated with individual current use of antifungals, as compared to non-use, were 1.2 for griseofulvine, 2.6 for fluconazole, 2.8 for terbinafine, and 3.9 for itraconazole. All these relative risks were based on a very small number of exposed cases, between one and four, and the confidence intervals were wide, not statistically significant, and overlapped among them.

The selected skin disorders assessed in this study are those commonly considered as potentially severe or life-threatening. However, the potential for severity is highly variable among the different disorders and also within a same condition. Toxic epidermal necrolysis is perhaps the most severe dermatosis and we did not identify any case neither in exposed nor in non-exposed patients.

Most of the cases identified in this study were not severe enough to require hospitalization and none was life-threatening. Only two cases of angioedema, which occurred among non-users of antifungals, had to be hospitalized. All exposed cases were treated by the general practitioner or by the dermatologist. This indicates that se-

vere, life-threatening skin disorders associated with the use of oral antifungals are extremely rare.

A consideration to this study is the potential for misclassification of specific diagnostics. Although cases identified were validated by asking to the corresponding general practitioner confirmation of the diagnosis, we did not assess the clinical characteristics of the specific skin disorder. This could result in misclassification of diagnostics particularly among those cases not referred to the dermatologist. Also, some forms of cutaneous reactions are sometimes difficult to differentiate among them specially in those cases with mild severity. Thus, misclassification could occur between the diagnosis of erythema multiforme and mild forms of Stevens-Johnson syndrome.

We defined current use of antifungals as all the days of prescribed treatment plus an additional period of two weeks after the end of treatment. Most cutaneous adverse reactions to drugs occur during the first three or four weeks of treatment.[7] With the additional period of two weeks after the end of treatment we ensured the capture of disorders appearing at the very end of treatment. For past use of oral antifungals we considered a period of 90 days after the end of the current use time window. The rationale for including a period of past use in pharmacoepidemiological studies is to examine drug effects with late onset that is with a long latency period. However, it is considered that adverse cutaneous reactions to drugs mainly occur during the period of active treatment. Thus, attribution of cutaneous disorders to the past use of specific drugs is more problematic and difficult to interpret than attribution to, active treatment.

Regarding terbinafine the risk of skin disorders was about three times higher than the risk in non-users and similar to the risk of other antifungals. This relative risk lies in the very low range of risks of severe skin disorders associated to other drugs. In an international case-control study the highest relative risks of Stevens-Johnson syndrome and toxic epidermal necrolysis for drugs ususally used for short periods were 172 for sulfonamides, 160 for trimethroprim-sulfamethoxazole, 62 for chlormezanone, 14 for cephalosporins, 10 for quinolones, and 6.7 for aminopenicillines.[8] Among drugs used for months or years the highest relative risks were for anti-epileptics (RR between 25 and 90), oxicam NSAIDs (RR = 72), allopurinol (RR = 52), and corticosteroids (RR = 54).[8,9] The number of cases of Stevens-Johnson syndrome and epidermal necrolysis attributable to the use of medications ranged from 0.2 cases per million for aminopenicillines and tetracyclines, to 4.5 cases per million for sulfonamides.[8]

Conclusions

We conclude that cutaneous disorders associated with the use of oral antifungals in this study were all of mild severity and that the risk associated with the use of oral antifungals was slightly higher than the risk in non-users. The safety profile of terbinafine regarding cutaneous disorders is similar to other antifungals and in the very low range of risks associated with other drugs.

Authors' contributions

All authors contributed equally in the study design, review of patient profiles, case validation, and data analysis.

All authors read and approved the final manuscript.

Competing interests

Jordi Castellsague, Alberto Duque, and Susana Perez were employees of Novartis Pharmaceuticals at the moment of conducting this study and writing the corresponding manuscript.

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