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Stomatitis associated with the use of terbinafine

Introduction

The orally and topically active allylamine antifungal agent terbinafine has been approved for marketing in The Netherlands in March 1992. The drug interferes with the ergosterol biosynthesis via specific and selective inhibition of fungal squalene epoxidase, resulting in a deficiency of the cell wall and intracellular squalene. The latter is responsible for fungicidal action[1]. Terbinafine is effective in the treatment of onychomycosis and several other types of dermatomycotic infections.[2] Its spectrum includes a broad range of dermatophyte and some yeast species. Adverse drug reactions (ADRs) may occur in about 10 % of the patients treated with terbinafine, the majority being gastro-intestinal disorders (5%), and skin reactions (2-3%)[1,3]. The treatment of onychomycosis may last for 12 weeks.

Terbinafine is bound to plasma proteins to a great extent and metabolised extensively in the liver. Elimination takes place in urine (80%) and faeces.

Until January 1st 2002, the Netherlands Pharmacovigilance Centre Lareb received 10 reports of stomatitis, related to the use of terbinafine.

Reports

An overview of the reports that have been received by the Netherlands Pharmacovigilance Centre is provided in Table 1.

Table 1. reports of stomatitis associated with the use of terbinafine

Patient, Sex, age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, outcome
A F, 54	Terbinafine 250 mg od Not specified	Captopril, hydrochlothiazide	'Blisters in mouth'	3 days
B F, 52	Terbinafine 250 mg od Tinea pedis	Lanzoprazole Benzoic acid/ salicilic acid ointment	Stomatitis	Not reported
C M, 28	Terbinafine 250 mg od Onychomycosis	Oxazepam, pimozide	Stomatitis (tongue and palate)	8 days
D F, 34	Terbinafine 250 mg od Onychomycosis	Ethinyl estradiol/ gestoden	Stomatitis aphthous	Not reported
E F, 39	Terbinafine 250 mg od Onychomycosis		'Burning feeling tongue' taste disorder	2 days
F F, 42	Terbinafine 250 mg od Onychomycosis	Oxazepam	Glossitis / stomatitis Vision disturbances	2 days, recovered
G F, 52	Terbinafine 250 mg od Onychomycosis	Flucloxacilin Haloperidol Lithium Lorazepam Fluoxetine	Painful mouth, glossitis	3 days, recovered after stopping terbinafine
H F, 54	Terbinafine 250 mg od Onychomycosis	Fosinopril Paroxetine	Mucosal blisters, mouth	Not reported, recovered
J F, 74	Terbinafine 250 mg od Dermatophytosis, unspecified	Temazepam Piroxicam Betamethason cream	'Blisters in mouth', taste alteration	5 days, recovered
K F, 45	Terbinafine 250 mg od Not specified		'Blisters in mouth'	11 days

The time of onset of the ADRs reported, are rather analogues and ranges from 2 till 11 days (average 5.1days). Mean age of the patients was 47.4 years. Although captopril used by patient A and fluoxetine used by patient G as concomitant medication have been associated with stomatitis[5,6], the time of onset of the suspected ADRs in these patients is strongly suggestive for a causal relationship with terbinafine. Furthermore, in six patients, the indication for use of terbinafine was onychomycosis. This disorder, however, is not associated with mucosal lesions.

Other sources of information

Literature

A search in the Medline database revealed no information concerning the occurrence of terbinafine associated with stomatitis or glossitis. In a large postmarketing surveillance study among 25.091 patients, adverse events involving the gastrointestinal system were reported in 4.9%. The most common events included nausea, diarrhoea, abdominal pain and dyspepsia.[1]. However, neither glossitis nor stomatitis are mentioned in this publication.

Databases

A total number of 534 reports on terbinafine have been reported to our pharmacovigilance centre. In our data set terbinafine was not disproportionately associated with these ADRs.

At the end of the third quarter of 2001 9,888 reports on terbinafine were filed in the database of the WHO Monitoring Centre. The reporting odds ratio concerning the association between terbinafine and these joined ADR terms in the data set of the WHO Monitoring Centre was 1.21 (95% confidence interval 0.99-1.47)

Mechanism

The patho-physiology of stomatitis associated with terbinafine in not clear. Rarely, terbinafine has been associated with drug eruptions such as toxic epidermal necrolysis, erythema multiforme and Stevens Johnson Syndrome. Although mucosal lesions may be involved in these disorders, it is unlikely that these patients suffer from one of these ADRs, since any involvement of other organ systems was not reported.
A well-known ADR of terbinafine is the occurrence of taste disorders.[7,8] Whether or not a relation exists with the occurrence of stomatitis is not clear, although patient V also reports a 'metallic taste'.

Conclusion

The disproportional number of reports to the Netherlands Pharmacovigilance Centre, the description of the ADRs as well as the temporal relationship, are all highly indicative of a causal relation between the use of terbinafine and stomatitis. Also data from the WHO Monitoring Centre are supportive for this association.
Quality of the signal: Ten cases in the Lareb database point to terbinafine-related stomatitis with a mean latency of 5 days. This association has no pharmacological plausibility, but is supported by a statistically non-significant disproportionality (lower CI_{95} 0.99) in the WHO-database.

References
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