

Terbinafine and smell alterations

Introduction

Terbinafine is an antifungal agent belonging to the class of allylamine derivatives, which was registered in the Netherlands in the early 1990's. Terbinafine is available both as a topical (cream, lotion, spray) and as an oral formulation (tablets). The oral formulation is indicated *for the treatment of tinea capitis and onychomycosis caused by dermatophytes*. In addition it is indicated *for the treatment tinea corporis, tinea cruris and tinea pedis if the location, severity or extent of the infection justifies oral therapy* [1-6].

The pharmacological mechanism of action is based on the inhibition of squalene epoxidase, an enzyme present in the fungal cell membrane. Inhibition of squalene epoxidase results in decreased ergosterol synthesis and accumulation of squalene, causing fungal cell death [1-6]. Taste disorders are a well-known ADR of terbinafine [1-6].

Disorders of the smell are not described in the SmPC of terbinafine [1-6].

Hyposmia is a diminished smell function. Anosmia is an absent smell function.

Parosmia is an abhorrent odor perception either without an odorant stimulus (phantosmia) or with an odorant stimulus (distortion or troposmia). And dysosmia is a general term describing distortion of smell sensations.

Nasal and paranasal sinus disease, including rhinosinusitis, rhinitis (allergic and nonallergic), and nasal polyps, are the most common causes of olfactory dysfunction and/or anosmia. These conditions can interfere with olfaction through inflammation of the mucosa as well as overt obstruction [7].

The current observation describes the association between terbinafine and smell disorders.

Reports

On 20 November 2012 the database of the Netherlands Pharmacovigilance Centre Lareb contained 15 reports concerning smell disorders associated with the use of terbinafine. In seven cases the patient suffered from a disorder of smell without a taste disorder being present (see Table 1). In eight cases the patient suffered from both a smell and taste disorder (see Table 2).

Table 1. Reports of smell disorders associated with the use of terbinafine

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 60818 M, 61-70 years general practitioner	terbinafine 250mg od onychomycosis	pravastatin, acetylsalicylic acid, metoprolol	parosmia	1 day discontinued recovered
B 22263 F, 41-50 years general practitioner	terbinafine 250mg od tinea unguium	dydrogesterone	anosmia	5 weeks discontinued not reported
C 57830 F, 31-40 years specialist doctor	terbinafine 250mg od dermatomycosis, unspecified	amoxicillin/ clavulanic acid	hyposmia	3 days discontinued not yet recovered

D 59538 F, 31-40 years pharmacist	terbinafine 250mg od onychomycosis		parosmia	7 days no change not recovered
E 120095 F, 51-60 years consumer	terbinafine 250mg od fungal infection	estradiole, clemastine	smell alteration	2 days no change not recovered
F 121547 M, 41-50 years pharmacist	terbinafine 250mg od onychomycosis	fosinopril	anosmia	3 months no change not recovered
G 131120 M, 61-70 years general practitioner	terbinafine 250mg od onychomycosis	valsartan, tamsulosin	anosmia	26 days discontinued not recovered

Table 2. Reports of both smell and taste disorders associated with the use of terbinafine

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
H 14354 F, 41-70 years physician with own pharmacy	terbinafine 250mg od tinea unguium	lisinopril	taste loss, smell change	4 weeks discontinued not reported
I 15851 M, 51-60 years general practitioner	terbinafine 250mg od tinea unguium		gustatory sense diminished, smell change	7 weeks discontinued not reported
J 26186 M, 62 pharmacist	terbinafine 250mg od tinea unguium	simvastatin, paroxetine, omeprazole	taste loss, parosmia	1 week no change unknown
K 36704 M, general practitioner	terbinafine 250mg od		ageusia, anosmia	18 days discontinued not recovered
L 52058 F, 61-70 years general practitioner	terbinafine 250mg od tinea		taste loss, parosmia	15 days discontinued not recovered
M 78159 M, 41-50 years consumer	terbinafine 250mg od onychomycosis		anosmia, dysgeusia	4 months discontinued recovered with sequelae
N 130109 M, 61-70 years consumer	terbinafine 250mg od onychomycosis		anosmia, dysgeusia	5 months discontinued not recovered

Additional information about the cases is given below:

Patient A uses pravastatin, acetylsalicylic acid, metoprolol as concomitant medications, initiated after a percutaneous coronary stent was placed. Startdate of the concomitant medication is unknown. The SmPC of metoprolol mentions taste disorders but no disorders of smell [8]. Taste- and smell disorders are not mentioned in the SmPC of pravastatin or acetylsalicylic acid [9,10]. In the literature hyposmia is described for pravastatin [11].

Patient B uses dydrogesterone as concomitant medication. This drug was started on 04-06-1998. Terbinafine was started approximately two months later. Disorders of taste- or smell are not described in the SmPC of dydrogesterone [12].

Patient C uses amoxicillin/clavulanic acid as concomitant medication. This drug was started on the same date as the terbinafine and also withdrawn in the same month. Indication for use is unknown. Taste- and/or smell disorders are not

described in the SmPC of this product [13], however olfactory disorders are described as rare adverse effects of antibiotic therapy in the literature [14]. Patient E uses estradiol ovules and clemastine as concomitant medication with unknown start dates. Disorders of taste- or smell are not described in the SmPC of both drugs [15,16].

Patient F uses fosinopril as concomitant medication. However, this drug was started two months after the reaction had occurred. The SmPC of fosinopril mentions taste disorders but no disorders of smell [17].

Patient G remarks that he reported because he had not recovered four weeks after terbinafine had been discontinued. He used valsartan and tamsulosin as concomitant medication for almost four years before terbinafine was started. Disorders of taste- or smell are not described in the SmPC of both drugs [18,19]. Patient H uses lisinopril as concomitant chronic medication, with an unknown start date. The SmPC of lisinopril mentions taste disorders but no disorders of smell [20].

Patient J uses simvastatin, paroxetine and omeprazole as concomitant medication. Omeprazole was started 1.5 month prior to start of terbinafine. Start dates of simvastatin and paroxetine are unknown. Taste- and smell disorders are not mentioned in the SmPC of simvastatin or paroxetine [21,22]. The SmPC of omeprazole mentions taste disorders but no disorders of smell [23].

Other sources of information

SmPC

Smell disturbances are not described in the SmPC of various terbinafine tablets available on the Dutch market [1-6].

However, the US SmPC of terbinafine (Lamisil®) mentions the following: “*Smell disturbance, including loss of smell, has been reported with the use of Lamisil Tablets. Smell disturbance may be prolonged, or may be permanent. Discontinue Lamisil Tablets if smell disturbance occurs*” [24].

Literature

The Italian pharmacovigilance centre performed a study to identify major drug classes associated with taste and smell alterations reported to the Italian spontaneous adverse drug reaction (ADR) reporting database. For terbinafine for topical use taste and/or smell impairments were reported 17 times. In 14 cases there were only taste disturbances, in 2 cases only smell disturbances and in one case both taste and smell disturbances existed. Mean age of the patients was 53, 13 patients were females. The median time to event onset was 24 days (range 4–95 days). In six cases the ADR led to treatment discontinuation, and in five cases taste and smell impairments were detected after the end of scheduled therapy. Five reports indicated a resolved outcome after a period of 35–140 days from the end of terbinafine intake. Twelve reports displayed an ongoing outcome at the last available follow-up (median time to follow-up 12 days; range 1–81 days). The authors remarked that smell alterations are not labelled for terbinafine [25].

In a case-control study of potential risk factors of terbinafine induced taste loss, concurrent smell loss occurred in 12 cases (13.8%) and one (0.3%) control (odds ratio 57.8; 95% CI: 8.2–2475) [26].

In the UK a postmarketing surveillance study of oral terbinafine in the UK was performed in a large cohort. Taste disturbance was reported by 64 (0.6%) patients of all ages. Two patients also reported anosmia [27].

Villota Hoyos and González-Ruiz [28] describe a case of ageusia and hyposmia associated with use of terbinafine. A 47-year old woman with onychomycosis without other concomitant diseases or medication, was prescribed terbinafine at doses of 250 mg / day. After 4 weeks of treatment she reported a taste alteration and finally a total loss of taste. Concomitantly she reported a significant decrease of smell. Oropharyngeal examination revealed no abnormalities. It was decided to discontinue treatment with terbinafine and the patient recovered after 11 weeks.

There have also been studies who found no effect of terbinafine on smell function. For instance an assessment of terbinafine-induced taste loss found that olfactory function was within normal limits [29].

Databases

On 20 November 2012 the database of the Netherlands Pharmacovigilance Centre Lareb contained 15 reports of smell disorders associated with the use of terbinafine. These 15 reports all fall within the MedDRA High Level Term (HLT) *Olfactory Nerve Disorders*. The combined reporting odds ratio (ROR) for these 15 reports is disproportional, ROR =4.5 (95%CI 2.7-7.5).

The WHO database of the Uppsala Monitoring Centre contained reports of MedDRA Preferred Terms (PT) anosmia, parosmia and hyposmia, all of which were disproportionally present in the database.

Table 3. Reports of smell disorders associated with terbinafine in the Lareb database

Drug	High Level Term	Number of reports	ROR (95% CI)
Terbinafine	Olfactory Nerve Disorders	15	4.5 (2.7-7.5)

Table 4. Reports of smell disorders associated with terbinafine in the WHO database

Drug	Preferred Term	Number of reports	ROR (95% CI)
Terbinafine	Anosmia	128	8.2 (6.9-9.7)
	Parosmia	100	8.3 (6.8-10.1)
	Hyposmia	5	4.0 (1.7-9.6)
Combined		233	8.1 (7.1-9.2)

On December 5th 2012, the Eudravigilance database contained 115 reports of smell disorders in association with terbinafine, which was reported disproportionately (ROR = 13.8, 95% CI: 10.8 – 15.7). See table 5.

Table 5. Reports of smell disorders associated with terbinafine in the Eudravigilance database

Drug	Preferred Term	Number of reports	ROR (95% CI)
Terbinafine	Anosmia	78	14.9 (11.9 – 18.7)
	Parosmia	30	9.3 (6.5 – 13.4)
	Hyposmia	7	16.4 (7.6 – 35.1)
Combined		115	13.0 (10.8 – 15.7)

Prescription data

The number of patients using terbinafine in the Netherlands is shown in table 6 [30].

Table 6. Number of patients using terbinafine in the Netherlands between 2007 and 2011

Drug	2007	2008	2009	2010	2011
Terbinafine	99,821	97,327	96,594	94,280	94,697

Mechanism

The mechanism by which terbinafine causes smell disorders remains unknown. *Henkin* [11] describes three major ways in which drug-induced taste- and smell disorders can occur. Firstly, for smell, specific nasal mucus nasal proteins are involved for maintenance of olfactory receptors. Drugs that inhibit synthesis or function of proteins involved with receptor turnover, growth and nutrition will lead to receptor loss with subsequent loss of smell function. For both taste and smell zinc metalloproteins are critical to maintain normal receptor integrity. Any drug interfering with zinc metabolism may alter either taste, smell or both.

Secondly, chemical binding of the sensory stimulus to the receptor must occur with an intact, biochemically functioning molecule. Thirdly, subsequent to receptor binding, G-protein activation is involved in the initiation of the action potential which is transmitted to the central nervous system for sense appropriate integration of taste or smell.

It has been proposed that the taste-related effects associated with terbinafine reflect an inhibition of cytochrome P450 enzymes of receptors leading to an alteration of the signal transduction pathway [11] or an alteration of the structure or function of neurons deputed to taste sensing by interference with the cholesterol pathway [29]. One could speculate that since there is overlap in the mechanisms by which taste- and smell disorders occur, similar mechanisms might play a role in the development of smell disorders.

Discussion and conclusion

Lareb received 15 reports of smell disorders associated with the use of terbinafine. In seven cases the patient suffered from a disorder of smell without a taste disorder being present. In eight cases the patient suffered from both a smell and taste disorder. In two cases the patient recovered (with sequel) after cessation of terbinafine and one patient was recovering. In three cases terbinafine was withdrawn and the outcome was not reported. In five cases terbinafine had been withdrawn but the patient had not recovered at the time of reporting. The US SmPC described that smell disturbance may be prolonged, or may be permanent [24].

The association between terbinafine and smell disorders is disproportionately present in the Lareb and WHO- and Eudravigilance database. Smell disorders are also described as an adverse drug reaction in the literature, sometimes occurring together with taste disorders and sometimes without a taste disturbance [25-28].

Other possible explanations for the disorders of smell, like confounding by concomitant medication, are limited in the Lareb cases.

Based on the above, it should be considered to mention smell disorders in the Dutch SmPC of terbinafine.

- Smell disorders should be mentioned in the SmPC of terbinafine

References

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