1.1. Oral terbinafine and hearing disorders

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 [1-11].
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 [1-11].
The most common adverse drug reactions associated with oral terbinafine use include arthralgia, myalgia, skin reactions (erythema, urticaria) and several gastrointestinal disorders [1-11].

Hearing disorders can be divided into three main subtypes: conductive, perceptive or functional. Risk factors for hearing disorders include age, heredity, noises and medications [12]. Drug-induced hearing disorders are generally perceptive in nature and are associated with the use of several antibiotics, diuretics and platinum containing chemotherapies [13].

Reports

On October 18, 2010, the database of the Netherlands Pharmacovigilance Centre Lareb contained 6 reports concerning hearing disorders with the use of terbinafine.

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

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 12707 F, 61 – 70 years	terbinafine tablet 250mg 1dd1		hearing decreased	3 weeks no change not reported
B 17627 M, 31 – 40 years*	terbinafine tablet 250mg 1dd1 Dermatophytosis NOS		hearing decreased	2 months discontinued not reported
C 17629 F, 41 – 50 years	terbinafine tablet 250mg 1dd1 Onychomycosis		hearing decreased, tinnitus	18 days discontinued not reported
D 26301 M, 61 – 70 years*	terbinafine tablet 250mg 1dd1 Onychomycosis		hearing decreased, tinnitus	2 weeks discontinued not reported
E 53880 F, 70 years and older	terbinafine tablet 250mg 1dd1 - non-current drug Onychomycosis	risedronate lisinopril non-current drug, calci chew d3 - non-current drug, dipyridamole	headache insomnia hearing decreased asthenia	2 days no change unknown
F 93633 M, 61 – 70 years	terbinafine tablet 250mg 1dd 1 Onychomycosis		hearing decreased	6 months discontinued recovered with sequelae

* Reports for patients B and D were provided by the same reporter

Specific characteristics of the reports are discussed below.

Patient A, a female aged 61 – 70 years experienced a bilateral hearing loss of 30-60dB (pure tone audiometry, frequencies not specified) and 30-40dB (speech audiometry) respectively. Terbinafine was continued for three months after start of the complaints. Initially this patient also used topical miconazole, and urea 40% ointment. After follow up it was reported that she had not recovered 4.5 years after stopping terbinafine therapy.
Patient B, a male aged 31 – 40 years experienced a unilateral hearing loss on the left side (approximately 25dB at 500-1000-2000Hz, 50dB at 4000Hz and 80dB at 8000Hz). According to the specialist doctor, there was no other pathology that could explain the hearing loss. The duration of treatment with terbinafine was not reported.
Patient C, a female aged 41 – 50 years experienced a bilateral subjective hearing loss. No audiometry has been performed. Initially, the symptoms disappeared after 1 day, but during a second episode symptoms persisted until terbinafine was withdrawn. The patient recovered slowly. Other pathology cannot be ruled out, however, the patient has not regularly been exposed to loud noises. Terbinafine has been used for 1.5 months.
Patient D, a male aged 61 – 70 years experienced tinnitus (right ear) and a hearing loss of 50dB (frequencies not specified). He had not recovered at the time of notification after 2 months. The duration of treatment with terbinafine was not reported.
Patient E, a female aged 70 years and older with a history of osteoporosis (with vertebral collapse) and hypertension experienced hearing loss of unknown severity. Although risedronate is known to cause tinnitus in some patients (1.6% in a phase III clinical trial), hearing loss has not been reported. The duration of treatment with terbinafine was not reported.
Patient F, a male aged 61 – 70 years experienced hearing loss after 6 months of terbinafine use. Further details were not provided. He recovered with sequelae after withdrawal of terbinafine. Total treatment duration was nearly 12 months.

Other sources of information

SmPC

Hearing disorders of any kind are not mentioned in the SmPC for terbinafine-containing products [1-11].

Literature

A medline search revealed no publications on the possible association between terbinafine and hearing disorders. (MeSH terms: hypoacusis, tinnitus, deafness, hearing disorders).

Databases

On October 19, 2010, the database of the Netherlands Pharmacovigilance Centre Lareb contained six cases of hypoacusis in association with terbinafine, which was reported disproportionally (ROR=4.2, 95% CI: 1.9-9.6). The Lareb database contained two cases of tinnitus.
The WHO database of the Uppsala Monitoring Centre contained 83 reports of hearing disorders (see table 1). Of these disorders, hypoacusis was reported disproportionally, whereas tinnitus and deafness were not. Disproportionality for sudden hearing loss, hearing impaired and deafness unilateral was not assessed due to the low number of reports.

Table 1. Reports of hearing disorders associated with terbinafine in the WHO database

ADR (MedDRA PT)	Number of reports	ROR (95% CI)
Hypoacusis	17	1.9 (1.18 - 3.07)
Tinnitus	42	0.75 (0.55 – 1.01)
Deafness	20	0.73 (0.47 – 1.13)

ADR (MedDRA PT)	Number of reports	ROR (95% CI)
Sudden hearing loss	1	Not Applicable*
Hearing impaired	2	Not Applicable *
Deafness unilateral	1	Not Applicable *

* Due to the low number of reports

On October 19 the Eudravigilance database contained 36 reports of hearing loss associated with the use of terbinafine, of which 33 (92%) were classified as 'serious'. In addition tinnitus was reported 18 times. The median age of the patients was 56 years (range 23-87).

Prescription data

The number of patients using terbinafine in the Netherlands is shown in table 4.

Table 4. Number of patients using oral terbinafine in the Netherlands between 2005 and 2009 [14]

Drug	2005	2006	2007	2008	2009
Terbinafine	122,670	108,070	99,820	97,534	98,199

Mechanism

The mechanism through which terbinafine may induce hearing disorders is unknown. Since squalene epoxidase also has a role in human cholesterol synthesis, inhibition of this enzyme by terbinafine might result in decreased cholesterol levels in human cells. This hypothesis is strengthened by results of an *in vivo* study showing that terbinafine not only inhibited squalene epoxidase from Candida, but from rat liver as well, although inhibition in rat liver occurred at higher drug concentrations (Ki = 30nM for Candida and Ki = 77µM for rat liver) [15]. This difference in dissociation constants suggests a low effect on human cholesterol synthesis, yet a possible effect cannot be excluded. Cholesterol has an important role in the cell membrane of the outer hair cells of the cochlea and cholesterol depletion in the outer hair cells has been shown to reduce membrane capacitance and presumably also electromotility and otoacoustic emissions of these cells, and may thus lead to a decreased hearing function [16]. It should be noted that this is a theoretical hypothesis and raises the question why cholesterol lowering medication is not associated with hearing disorders.
In addition to hearing disorders, terbinafine is known to cause taste disorders [1-11], and there is support for the hypothesis that this effect is neurological and occurs at the level of the taste receptors [17]. In the WHO database, taste disorders were reported in 7 cases (8%) out of 83 cases of hearing disorders in patients using terbinafine.
The above may suggests that if there is a causal relationship between hearing disorders and terbinafine use, it is most likely of neurological origin.

Discussion

Lareb received 6 reports concerning hearing disorders with the use of terbinafine.
In two cases a positive dechallenge has been reported, although in one of those cases, the patient recovered with sequelae.

Latencies were rather inconsistent between cases, varying from two days to six months. This could partially be explained by the nature of the condition which is often not immediately recognized and diagnosed, and is more common in the elderly. Although a precise mechanism is unknown, cholesterol depletion seems to be associated with decreased electromotility and otoacoustic emissions of outer hair cells of the cochlea. It should be noted however, that a latency of two days as reported in case E is rather unlikely under this hypothesis.

The association between hearing disorders is supported by a statistically significant disproportionality in the database of the Netherlands Pharmacovigilance Centre Lareb. The WHO database contains a disproportionate number of reports for hypoacusis associated with terbinafine use, however, other hearing disorders (mainly deafness and tinnitus) were not present disproportionately. This may partially be explained by underreporting of hearing disorders, due to possibly long latencies.
In 1997, a publication of two case reports in “Geneesmiddelenbulletin”, regarding hearing loss and terbinafine use, may have led to notoriety bias [18]. A review of the individual reports shows that two of the cases were reported in 1997. The remaining four cases were reported in 1995, 1999, 2005 and 2009.

Conclusion

These cases suggest a signal of hearing disorders associated with the use of terbinafine.

- Possible new signal of terbinafine associated with hearing disorders. It should be considered to mention hearing disorders in the SmPC of terbinafine

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This signal has been raised on April 2011. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).