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Hearing Impairment Associated with Oral Terbinafine Use

A Case Series and Case/Non-Case Analysis in the Netherlands Pharmacovigilance Centre Lareb Database and VigiBase™

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Abstract

Background: The Netherlands Pharmacovigilance Centre Lareb received reports of six cases of hearing impairment in association with oral terbinafine use. This study describes these cases and provides support for this association from the Lareb database for spontaneous adverse drug reaction (ADR) reporting and from Vigibase™, the ADR database of the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre.

Objectives: The objective of the current study was to identify whether the observed association between oral terbinafine use and hearing impairment, based on cases received by Lareb, constitutes a safety signal.

Methods: Cases of hearing impairment in oral terbinafine users are described. In a case/non-case analysis, the strength of the association in Vigibase™ and the Lareb database was determined (date of analysis August 2011) by calculating the reporting odds ratios (RORs), adjusted for possible confounding by age, sex and ototoxic concomitant medication. For the purpose of this study, RORs were calculated for deafness, hypoacusis and the combination of both, defined as hearing impairment.

Results: In the Lareb database, six reports concerning individuals aged 31–82 years, who developed hearing impairment after starting oral terbinafine, were present. The use of oral terbinafine was disproportionally associated with hypoacusis in both the Lareb database (adjusted ROR 3.9; 95% CI 1.7, 9.0) and in Vigibase™ (adjusted ROR 1.7; 95% CI 1.0, 2.8). Deafness was not disproportionally present in either of the databases.

Discussion: Based on the described cases and the statistical analyses from both databases, a causal relationship between the use of oral terbinafine and hearing impairment is possible. The mechanism by which terbinafine could cause hearing impairment has not been elucidated yet. The pharmacological action of terbinafine is based on the inhibition of squalene epoxidase, an enzyme present in both fungal and human cells. This inhibition might result in a decrease in cholesterol levels in human cells, among which are the outer hair cells of the cochlea. It may be possible that the reduction in cochlear

cholesterol levels leads to impaired cochlear function and possibly hearing impairment.

Conclusion: In this study we describe hearing impairment as a possible ADR of oral terbinafine, based on six case reports and statistical support from Vigibase™ and the Lareb database. To our knowledge this association has not been described before.

Background

Hearing impairment can be a severely debilitating condition with a possible negative effect on quality of life and psychosocial status.[1] Objective hearing impairment can be divided into three main categories: conductive, sensorineural and a combination of both (mixed). In addition to these three types of objective hearing impairment, patients can experience subjective or functional hearing impairment, which is mostly psychological or psychiatric in origin.

Although the aetiology of hearing impairment is not always known, several risk factors have been identified, including age, heredity, exposure to loud noises and use of medicines.

Medicine-induced hearing impairment is generally sensorineural in nature and is associated with the use of several classes of drugs, including antimalarials, aminoglycosides and other antimicrobial agents, loop diuretics, antineoplastic drugs and chelating agents.[2]

Terbinafine is an antifungal agent belonging to the class of allylamine derivatives, and is generally available both as a topical and oral formulation. Terbinafine may be used for various indications, including onychomycosis and (mild) fungal infections of the skin. Between the years 2006 and 2010, approximately 100 000 patients (≈0.6% of the total population) were exposed to the oral formulation of terbinafine in the Netherlands.[3]

The aim of our study is to describe the cases of hearing impairment associated with oral terbinafine use present in the database of the Netherlands Pharmacovigilance Centre Lareb (Lareb), and to study the strength of this signal in its database, as well as in Vigibase™, the database of the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (WHO-UMC).

Methods

Lareb maintains the spontaneous adverse drug reaction (ADR) reporting system in the Netherlands. The reports submitted to Lareb are described and reports from Vigibase™ are summarized. Subsequently, the reports submitted to Lareb and Vigibase™ are quantitatively analysed. Currently, the Vigibase™ database contains over 6.6 million ADR reports from more than 130 countries.

For the purpose of this analysis, ADRs are coded according to the Medical Dictionary for Regulatory Activities (MedDRA®; version 14.0) and the suspected drugs are classified according to the WHO Anatomical Therapeutic Chemical (ATC) classification system. All ADRs reported to Lareb up to 7 July 2011 and to Vigibase™ up to 31 March 2011 were taken into account for this analysis. The index group consisted of reports with the suspected drug being an oral formulation of terbinafine (ATC code D01BA02). Since systemic exposure of the topical formulations is less than 5%,[4-6] only reports with oral terbinafine were taken into account.

Reports of patients using suspected or concomitant medications for conditions of the outer ear and ear canal (ATC codes starting with S02 and S03) were excluded. The control group consisted of all other reports in the database. Cases were defined as reports mentioning MedDRA® Preferred Terms (PT) that reflect hearing impairment. Since hearing impairment includes the entire spectrum from slightly decreased hearing to complete deafness, we divided the reported events into two categories: deafness and hypoacusis.

This division was based on the PT that was assigned to the reported event. The following PTs, with corresponding PT codes, were defined as deafness: deafness, 10111878; deafness bilateral, 10052556; deafness neurosensory, 10011891; deafness permanent, 10011894; deafness transitory, 10011900; deafness unilateral, 10048812; mixed deafness, 10027757; sudden hearing impairment, 10061373. For hypoacusis, the PTs with corresponding codes were hearing impaired, 10019245; hypoacusis, 10048865; neurosensory hypoacusis, 10067587; presbyacusis, 10036626.

Since oral terbinafine treatment is not indicated in patients younger than 2 years, reports of patients belonging to that age group were excluded. All other reports, with the exception of reports of patients younger than 2 years of age, which were excluded, were classified as non-cases.

The strength of the association between hearing impairment and the use of oral terbinafine, compared with other drugs in both the Lareb database and Vigibase™ was calculated using the ADR reporting odds ratio (ROR), with corresponding 95% confidence intervals (CI) as a measure of disproportionality.[7] Unadjusted and adjusted RORs were calculated by means of logistic regression analysis. In instances where the ROR is statistically significant, hearing impairment is more frequently reported in association with oral terbinafine compared with the other drugs present in the database. In order to make the data of Lareb and Vigibase™ more easily comparable, measures of disproportionality of Vigibase™ (Bayesian Confidence Propagation Neural Network [BCPNN]) were converted to RORs. In addition, logistic regression analysis, by which the strength of the association is expressed as an odds ratio, enables adjustment for possible co-variates. A study by van Puijenbroek et al.[8] showed that various measures of signal detection (including ROR and BCPNN) are comparable in terms of sensitivity and specificity, when the number of reports for a certain drug-ADR association is four or more.

Age, sex and the presence of suspected or concomitant drugs that have been associated with hearing impairment in the literature, were used as co-variates. In a study by Raynor et al.,[9] an increase in hearing impairment was found with increasing age. Based on these data, we identified three age classes that were used as an ordinal variable in our study (2–64 years, 65–74 years, and 75 years and older). Concomitant medication that has been associated with hearing impairment was defined as any drug considered concomitant by the reporter that had been identified as ototoxic in recent literature. For this identification, two review articles from 2006 by Schacht and Hawkins[2] and Yorgason et al.[10] were consulted, resulting in a detailed list of ototoxic drugs (see table I). For statistical analysis, the software package SPSS 15.0 (SPSS Corporation, Chicago, IL, USA) was used.

Results

Between the date of approval of terbinafine in the Netherlands (early 1990s) and 7 July 2011,

Table I. Drugs, including Anatomical Therapeutic Chemical classification codes that have been associated with hearing impairment

ATC code	Drug name
P01BC	Quinine
P01BA	Chloroquine
M01AE	Propionic acid and derivatives
M01AB01	Indomethacin
M01AB02	Sulindac
M01AA01	Phenylbutazone
N02BA	Salicylates
J01GA	Sterptomycines
J01GB	Other aminoglycosides
J01FA	Macrolides
J01XB01	Colistin
J01AA08	Minocyclin
J01XA01	Vancomycin
C03CA01	Furosemide
C03CA02	Bumetanide
D08AC02	Chlorhexidine (topical)
L01DC01	Bleomycin
L01XA01	Cisplatin
L01XA02	Carboplatin
L04AX03	Methotrexate
L01AA	Nitrogen mustard derivatives
L01CA01	Vinblastine
L01CA02	Vincristine
V03AC01	Deferoxamine

ATC = Anatomical Therapeutic Chemical.

Lareb received six reports of cases of hearing impairment associated with the use of oral terbinafine. The characteristics of the below-described cases are summarized in table II.

Patient A (report date 1995) was a 64-year-old female with no known medical history who was treated with oral terbinafine 250 mg once daily for onychomycosis. Three weeks after the start of terbinafine she experienced a bilateral hearing impairment of 30–60 dB (pure tone audiometry, frequencies not specified) and 30–40 dB (speech audiometry). In addition to her hearing impairment she also reported tinnitus. Since hearing impairment and tinnitus were both unknown ADRs of terbinafine, the medication was continued for 3 months. Initially, the patient also used topical miconazole and urea 40% ointment. She had not recovered 4.5 years after stopping terbinafine therapy.

Patient B (report date 1997) was a 31-year-old male with no known medical history who experienced a perceptive, unilateral hearing impairment on the left side 2 months after starting terbinafine 250 mg once daily for dermatophytosis. The hearing impairment was approximately 25 dB at 500/1000/2000 Hz, 50 dB at 4000 Hz and 80 dB at 8000 Hz. Magnetic resonance imaging showed no retrocochlear pathology, and other pathologies that could have caused the hearing impairment could not be confirmed. After a total treatment duration of 3 months, terbinafine was withdrawn. At the time of reporting, approximately 1 year after withdrawal of terbinafine, the patient had not yet recovered.

Patient C (report date 1997) was a 48-year-old female with no known medical history who experienced tinnitus and a bilateral hearing impairment of unknown severity. She had been using terbinafine 250 mg once daily for onychomycosis for 18 days when the symptoms first presented. Initially, she recovered within 1 day despite continuation of terbinafine. During a second episode of both tinnitus and hearing impairment, which occurred approximately 4 weeks later, the symptoms persisted until terbinafine was withdrawn. After withdrawal the patient recovered slowly but fully. The total treatment duration with terbinafine was approximately 1.5 months. In this case no audiometry was performed, and although other pathology cannot be ruled out, the patient had not regularly been exposed to loud noises and did not have a profession or any hobbies that could have caused or aggravated the symptoms.

Patient D (report date 1999) was a 63-year-old male with no known medical history who experienced perceptive hearing impairment and unilateral tinnitus (right ear) 2 weeks after starting oral terbinafine 250 mg once daily for onychomycosis. Pure tone audiometry showed a hearing impairment of approximately 40–50 dB of the right ear at all frequencies. On the left side, the impairment was approximately 25 dB at 2000 Hz, 35 dB at 4000 Hz and 50 dB at 8000 Hz. These results were confirmed by speech audiometry. Terbinafine was withdrawn and the patient had not recovered at the time of notification 2 months later. The duration of treatment with terbinafine was 4.5 weeks.

Patient E (report date 2005) is an 82-year-old female who experienced a hearing impairment of unknown severity in combination with headache, insomnia and asthenia. She had taken terbinafine

Table II. Characteristics of the described cases

Patient	Age (y)	Sex	Latency	Withdrawal (Yes/No)	Outcome
A	64	Female	3 weeks	Yes	Not recovered
B	31	Male	2 months	Yes	Not recovered
C	48	Female	18 days	Yes	Recovered[a]
D	63	Male	2 weeks	Yes	Not recovered
E	82	Female	2 days	Not reported	Not reported
F	65	Male	6 months	Yes	Recovered with sequelae

a Patient recovered from an initial episode (latency 18 days) while continuing terbinafine, and from a second episode (which started 4 weeks after the first episode) after withdrawal of terbinafine.

Table III. Reporting odds ratios and corresponding 95% confidence intervals from VigiBase™ and the Lareb database for hearing impairment associated with the use of oral terbinafine

Reported ADR	Lareb database (6 cases)		VigiBase™ (28 cases)	
	ROR unadjusted	ROR adjusted[a]	ROR unadjusted	ROR adjusted[a]
Hearing impairment	NA[b]	NA[b]	0.8 (0.6, 1.2)	0.9 (0.7, 1.4)
Hypoacusis	3.8 (1.7, 8.7)	3.9 (1.7, 9.0)	1.5 (0.9, 2.5)	1.7 (1.0, 2.8)
Deafness	NA[b]	NA[b]	0.5 (0.3, 0.9)	0.6 (0.3, 1.0)

a Adjusted RORs were adjusted for age, sex and the presence of suspected or concomitant drugs that have been associated with hearing impairment.

b No RORs could be determined for deafness since the Lareb database did not contain any reports of deafness associated with the use of oral terbinafine. As a result, the combined ROR for deafness and hypoacusis was also not calculated.

ADR = adverse drug reaction; **NA** = not applicable; **ROR** = reporting odds ratio.

250 mg once daily for onychomycosis for 2 days when the symptoms first presented. It was not reported whether the hearing impairment was unilateral or bilateral. The patient's medical history mentions hypertension and osteoporosis with a vertebral collapse. She was treated for osteoporosis with risedronic acid 35 mg once weekly and cholecalciferol/calcium carbonate 1.25 g once daily. She was also taking lisinopril 5 mg daily for hypertension and dipyridamole for an indication that was not stated in the report. The report did not indicate whether, and when, treatment with terbinafine was ceased and whether, and when, recovery from the hearing impairment occurred.

Patient F (report date 2009) was a 65-year-old male with no known medical history who experienced a hearing impairment of unknown severity 6 months after starting oral terbinafine 250 mg once daily for onychomycosis on his right thumb. It was not reported whether the hearing impairment was unilateral or bilateral. After withdrawal of terbinafine, which he had been using for approximately 1 year, he recovered with sequelae. The extent of the sequelae was not reported.

Disproportionality Analysis

Vigibase™

Up to 31 March 2011, a total of 11 739 reports with oral terbinafine as the suspected drug were received in which the sex and age of the patient was specified. Hearing impairment as the suspected ADR was reported in 28 (0.24%) of the reports. It concerned 13 females and 15 males with a median age of 56 years (range 17–86 years). Latencies varied from 1 day to 11 months. In 14 cases, both the action taken with terbinafine and the outcome were reported. In six of these, there was a positive dechallenge, six patients did not recover and one patient recovered with sequelae after withdrawal of terbinafine, and one patient continued treatment with terbinafine and did not recover. A causality assessment was present in eight cases. In two cases the causality was reported as 'probable', whereas a 'possible' and 'unlikely' causality were both reported three times.

Of these reports, the reported ADR was defined as hypoacusis in 16 cases and as deafness in 12 cases. One of these cases mentioned the use of concomitant medication that has been associated with hearing impairment in the literature. Logistic regression analysis showed that the use of oral terbinafine was statistically significantly associated with hypoacusis (unadjusted ROR 1.5; 95% CI 0.9, 2.5; adjusted ROR 1.7; 95% CI 1.0, 2.8), but not with deafness or the combination of both (see also table III).

Netherlands Pharmacovigilance Centre Lareb Database

On 7 July 2011 the Lareb database contained a total of 849 reports describing one or more ADRs associated with the use of terbinafine. Of these reports, six (0.71%) included a PT within our category of hypoacusis. In none of these reports, the use of ototoxic concomitant medication was reported. Logistic regression analysis showed that the use of oral terbinafine was statistically significantly associated with hypoacusis (unadjusted ROR 3.8; 95% CI 1.7, 8.7; adjusted ROR 3.9; 95% CI 1.7, 9.0). Since the Lareb database

did not contain reports regarding deafness in association with oral terbinafine, the ROR for this association, as well as for the combined deafness/hypoacusis association was not determined (see also table III).

Discussion

This study describes six patients who developed a hearing impairment, possibly associated with the use of oral terbinafine. Data from Vigibase™ and the Lareb database support this association for patients experiencing hypoacusis, although the results from Vigibase™ are less convincing than those from the Lareb database, but not for deafness. It is important to note that the cases from Vigibase™ contain the cases from the Lareb database described in this article.

One of the major indications for prescribing terbinafine is onychomycosis, which is generally cosmetic in nature; hypoacusis is currently not labelled in the Summary of Product Characteristics (SPC) of oral formulations of terbinafine.

These cases originated from a spontaneous reporting system for ADRs, which is based on experiences in everyday practice. The information provided by the reporter can be subjected to bias. The reports of patients B and D originated from the same reporter, which may have led to reporting bias. Unfortunately, detailed case descriptions were not available for all cases, despite our efforts to obtain this information.

In cases A, B, D and F, treatment with terbinafine was continued after the initial symptoms of hearing impairment presented. In cases A, B and D the patient had not recovered at the time of notification, and patient F recovered with sequelae, of which the extent was not reported. Although patient B experienced a unilateral hearing impairment, indicating that it is most likely not drug-induced, a causal relationship cannot be excluded. Initially, patient C recovered shortly after the symptoms presented (while continuing terbinafine) and recovered from a second episode after withdrawal of terbinafine. For patient E, the relevant information regarding outcome of the event was not provided. Based on the above, there does not seem to be a relationship between total treatment duration and outcome of the episode of hearing impairment.

We found that, in most cases, reported latencies of onset of hearing impairment were rather long, and it is possible that this may have resulted in selective underreporting. In order to test this hypothesis, we carried out an additional analysis to compare the time of onset of the cases, with the latencies of all other reports containing oral terbinafine as the suspect drug in Vigibase™. This analysis showed a mean latency of 61 days (range 0.5–180 days) for cases in which hearing impairment has been reported and of 45 days (range 0.5–3650 days) for all other cases. The observed difference of 16 days was not statistically significant ($p > 0.05$), which may be due to the large range observed in the hearing impairment cases.

The mechanism by which terbinafine could cause hearing impairment has not been elucidated yet. The pharmacological action of terbinafine is based on the inhibition of squalene epoxidase, an enzyme present in the fungal cell membrane. Inhibition of this enzyme results in decreased ergosterol synthesis, accumulation of squalene and subsequently in fungal cell death.[11] In human cells, squalene epoxidase also has a role in sterol biosynthesis. Together with squalene cyclase, it converts squalene into lanosterol[12] and inhibition of this enzyme might result in decreased cholesterol levels in human cells. This hypothesis is supported by results of an *in vivo* study showing that terbinafine inhibited squalene epoxidase from both Candida albicans ($K_i = 39$ nM) and rat liver ($K_i = 77$ μM).[13] Although this difference in dissociation constants suggests a minor effect on human cholesterol synthesis, the possibility cannot be excluded.

Mammalian (and thus human) hearing is powered by cochlear outer hair cell (OHC) electromotility, a membrane-based motor mechanism present in the OHC lateral wall.[14] Studies suggest that these lateral wall membranes contain less cholesterol than the apical and basal membranes,[15-18] and results of animal experiments have shown that changes in cholesterol levels in the cochlea influence OHC membrane capacitance and otoacoustic emissions.[14] These data may imply that a reduction in cholesterol levels could lead to an impaired cochlear function and ulti-

mately to hearing impairment. The plausibility of the above-described pharmacological mechanism is strengthened by the fact that hearing impairment has been associated with the use of the cholesterol-lowering drug atorvastatin.[19] Although, to our knowledge, the distribution of terbinafine within the cochlea has not been described in literature, exposure of this organ seems plausible based on the large distribution volume of terbinafine.[20]

Although our present findings do not undeniably prove causality, they are suggestive of a possible relationship between terbinafine and hearing impairment. Also, the current findings may alert healthcare professionals to the possibility of terbinafine-induced hearing impairment and may lead to additional evidence for this association.

Conclusions

In this study we describe hearing impairment as a possible ADR of oral terbinafine, based on six case reports and the fact that this association is disproportionally present in both the Lareb database and Vigibase™. To our knowledge this association has not been described before in the literature and is not mentioned in the SPC of oral formulations of terbinafine.

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