

Oral terbinafine and erectile dysfunction

Introduction

Terbinafine (Lamisil®) 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].

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].

Erectile dysfunction has been defined as the persistent inability to reach or maintain penile rigidity enough for sexual satisfaction. Erectile dysfunction has a high prevalence and a huge impact on quality of life of men and their partners. Common risk factors associated with sexual dysfunction include individual general health status, diabetes mellitus, cardiovascular disease, other genitourinary disease, psychiatric/psychological disorders, other chronic diseases, socio-demographic conditions and the use of certain drugs [2].

Reports

In the period from June 1st 1995 until October 22nd 2014, Lareb received seven reports of erectile dysfunction associated with the use of oral terbinafine. The reports are listed in table 1.

Table 1. Reports of erectile dysfunction 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 14836 M, 61-70 years General practitioner	terbinafine 250 mg 1dd	captopril	impotence libido decreased	1 month discontinued recovered
B 15800 M, 61-70 years General practitioner	terbinafine 250 mg 1dd		impotentia erigendi	1 day discontinued recovered, positive rechallenge
C 20861 M, 51-60 years General practitioner	terbinafine 250 mg 1dd tinea unguium		impotentia erigendi	several days discontinued recovered
D 29485 M, 61-70 years Pharmacist	terbinafine 250 mg 1dd dermatophytosis		impotence	several hours discontinued not recovered
E 37165 M, 41-50 years General practitioner	terbinafine 250 mg 1dd tinea unguium		erection decreased	3 months no change not recovered
F 38764 M, 51-60 years	terbinafine 250 mg 1dd tinea unguium		erection decreased	6 weeks no change not recovered

Pharmacist				
G 166557 M, 61-70 years General practitioner	terbinafine 250 mg 1dd mycosis	selenium sulphide (cutaneous)	erection decreased gynaecomastia	4 months discontinued recovered

Patient A experienced the complaints prior to starting captopril, which is associated with erectile dysfunction.

Patient B had a positive dechallenge and a positive rechallenge.

Patient C experienced similar complaints while using itraconazole in the past (approximately 1.5 years prior to the current episode)

For patient G, the complaints disappeared immediately (not further specified) after withdrawal of terbinafine. For patients A, B, C, no information regarding the time to recovery after withdrawal of terbinafine was provided.

Other sources of information

SmPC

Erectile dysfunction or related ADRs, are not mentioned in the Dutch SmPC of terbinafine [1].

Literature

One previous case of erectile dysfunction associated with terbinafine was found in the literature. It concerns a 40-year-old man who was treated with terbinafine for a granulomatous plague of the left shin, from which *Sporolhrix schenckii* was isolated. The patient reported that, during treatment with terbinafine, it took him longer to attain a penile erection which, furthermore, was of poor quality and consequently had adverse effects on his sexual performance (orgasm and ejaculation were normal). The complaints started one week after starting terbinafine and returned to normal on completion of the treatment. The total duration of treatment with terbinafine was 12 weeks [3].

Databases

Table 2. Number of reported cases of erectile dysfunction associated with the use of terbinafine in the databases of the Netherlands Pharmacovigilance Centre Lareb [4], WHO [5] and Eudravigilance (EMA) [6].

Database	Preferred Terms	Number of reports	ROR (95% CI)
Lareb	Erectile dysfunction	7	1.2 (0.6 – 2.5)
WHO	Erectile dysfunction	57	1.2 (0.9 – 1.6)
Eudravigilance	Erectile dysfunction	12*	0.8 (0.4 – 1.4)

* Only 1 case (the most recent one) from Lareb is present in the Eudravigilance database. This is due to the fact that most reports were received prior to the date when exchange between Lareb and Eudravigilance was possible (approximately around 2004).

Prescription data

Table 3. Number of patients using terbinafine in the Netherlands between 2009 and 2013 [7].

Drug	2009	2010	2011	2012	2013
Terbinafine	96,594	94,280	94,767	93,731	88,859

Mechanism

The physiological mechanism of penile erection is complex and consists of neural, vascular, sinusoidal, and muscular components. In this process, several central and peripheral regulators are involved, including serotonin, dopamine, acetylcholine, oxytocin, noradrenalin, GABA, nitric oxide (NO), endothelins, and several additional factors [8]. No association between these factors, terbinafine and erectile dysfunction could be found in the literature.

For the antifungal agent ketoconazole, it is known that its use is associated with a decrease in testosterone levels, especially when higher doses are administered. In a previous quarterly report describing the association between itraconazole and erectile dysfunction, an interference with testosterone synthesis could not be found [9]. For terbinafine such an effect has not been observed either [10,11]. Additionally, in vitro research showed that, although terbinafine has some inhibitory effect on the hydroxylation of ethinylestradiol (suggesting a possible effect on the estrogen metabolism), it is unlikely that this is relevant in clinical use [12].

Discussion and conclusion

Lareb received seven reports of erectile dysfunction associated with the use of terbinafine, with positive dechallenges reported in four of them and a positive rechallenge in one patient. Latencies ranged from several hours to approximately four months. Since erectile dysfunction can have several causes (e.g. psychological, neural, vascular, hormonal) and no pharmacological mechanism for terbinafine induced erectile dysfunction could be found in literature, it is difficult to determine which latencies could be supportive of a causal relationship. Although age should be considered as a confounder in patients experiencing erectile dysfunction, the fact that a positive dechallenge was reported in approximately 50% of the cases, seems to weaken this hypothesis.

In the scientific literature one case of terbinafine associated erectile dysfunction was found, reported in a small cohort of five patients. The case shows similarity with the Lareb cases regarding latency (1 week) and the presence of a positive dechallenge.

- Further investigation of the information of the marketing authorization holders and other national centres is needed to strengthen the signal

References

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This signal has been raised on March 2015. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbq-meb.nl