

Objective Assessment of Terbinafine-Induced Taste Loss

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Objectives: Terbinafine (Lamisil), a widely prescribed oral antifungal agent, reportedly induces taste loss in 0.6% to 2.8% of those taking the drug. However, many so-called taste problems reflect olfactory problems, and the sole empirical study published on this topic, based on whole-mouth testing of a single subject, found no terbinafine-related deficit. In this study, we quantitatively assessed, using well-validated taste and smell tests, chemosensory function in six patients complaining of taste disturbance after terbinafine treatment and compared their test scores to those of six age-, race-, and sex-matched normal controls. **Methods:** Taste function was measured using a 96-trial regional test that assesses sweet, sour, bitter, and salty taste perception within the anterior (cranial nerve [CN] VII) and posterior (CN IX) lingual taste bud fields. Smell function was bilaterally evaluated using the 40-item University of Pennsylvania Smell Identification Test. **Results:** Taste function for sweet-, sour-, and bitter-tasting stimuli was significantly depressed in both the anterior and posterior lingual regions. For sodium chloride, the decrements were confined to the posterior region. Olfactory function was within normal limits. **Conclusion:** These findings 1) support anecdotal case reports of taste loss after terbinafine use, 2) demonstrate that all four major taste qualities are affected, and 3) suggest that olfactory dysfunction is not involved. Because self-report markedly underestimates chemosensory deficits, more extensive quantitative testing of patients receiving terbinafine will likely reveal a much higher prevalence of terbinafine-induced taste loss than currently reported. Since being older than

65 years of age and having a low body mass index are reportedly risk factors for terbinafine-induced taste loss, physicians should be particularly on the alert for elderly persons taking this medication who may become depressed or alter their food intake in response to decreased taste sensation.

Laryngoscope, 115:2035–2037, 2005

INTRODUCTION

Terbinafine (Lamisil), an oral antimycotic widely used to treat finger and toenail fungal infections, reportedly induces taste loss in 0.6% to 2.8% of those taking the drug.¹ Case reports suggest that taste loss commonly occurs after 4 to 6 weeks of drug use.^{2,3} Subjective recovery is said to occur after 4 months of symptom onset, although long-lasting losses have been reported.^{1,2,4} However, despite the numerous reports of terbinafine-related taste disturbances, only one study has quantitatively assessed taste function, and this study found normal whole-mouth thresholds in the sole patient tested.⁵ Surprisingly, no formal olfactory evaluation has been made of patients complaining of terbinafine-related taste problems, despite the well-documented tendency to misidentify olfactory disturbances as taste disturbances⁶ and the possibility that both taste and smell may be altered by this agent.

MATERIALS AND METHODS

Between April, 1999, and October, 2004, eight patients presented to the Smell and Taste Center with complaints of chemosensory disturbance temporally related to Lamisil use in the standard dosage (250 mg/d). Two were excluded from this study because of confounding factors (chronic rhinosinusitis and otitis media with cholesteatoma). The remaining six (3 female and 3 male nonsmokers) were 44 to 83 years of age (mean [SD] 60.67 years [14.98]). Nasal endoscopy revealed no discernible pathology. For comparison purposes, six age-, sex- and smoking-habit-matched subjects with no reported chemosensory deficits were given equivalent tests. All subjects provided written informed consent, in accord with the regulations of the University's Office of Regulatory Affairs.

Taste assessment was made using a well-validated regional taste test that assesses anterior (cranial nerve [CN] VII) and posterior (CN IX) taste function. In this test, 15 μ L of single concentrations of sucrose (0.49 M), sodium chloride (0.31 M), citric acid (0.015 M), and caffeine (0.04 M), equated for psychologic intensity and physical viscosity (1.53 mm²/s²), are presented to selected tongue regions using an Eppendorf pipette. On each

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Disclosure: Dr. Doty is a major shareholder in Sensonics, Inc., the manufacturer of the smell test that was used in this study.

Supported, in part, by Grants RO1 DC 04278, RO1 DC 02974, and RO1 AG17496 from the National Institutes of Health, Bethesda, Maryland, U.S.A.

Editor's Note: This Manuscript was accepted for publication July 21, 2005.

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DOI: 10.1097/01.MLG.0000181462.08683.0C

trial, the subject indicates whether a given stimulus tastes sweet, sour, bitter, or salty by pointing to alternative answers on a chart before protracting the tongue and rinsing the mouth with purified water. A total of 96 trials are used (4 tastants \times 6 trials \times 4 tongue regions). Olfaction was bilaterally evaluated using the University of Pennsylvania Smell Identification Test (UPSIT), a widely used standardized test of olfactory function.⁷ On this test, the subject is required to identify, from a list of 4 alternatives for each of 40 microencapsulated odorants, the name of the odor that is smelled.

RESULTS

The data for each tastant were subjected to an analysis of covariance (age = covariate), with group (terbinafine, control) as a between-subject factor and tongue region (anterior left, anterior right, posterior left, posterior right) as a within-subject factor. In all cases, a significant group effect emerged. As shown in Figure 1, the mean taste test scores were significantly lower in the terbinafine than in the control group for all stimuli, with sour (citric acid) and bitter (caffeine) perception being altered more severely than sweet (sucrose) and salty (NaCl) perception. A tongue region by group interaction approached significance for NaCl ($P = .07$), reflecting poorer performance on the posterior (CN IX) regions of the tongue (Fig. 2). A nonsignificant positive correlation was present between the test measures and the length of time since treatment cessation (Pearson $r = 0.52$, $P = .29$). No influence of terbinafine on UPSIT scores was found (respective mean [SEM] terbinafine and control values 35.01 [2.0] and 32.49

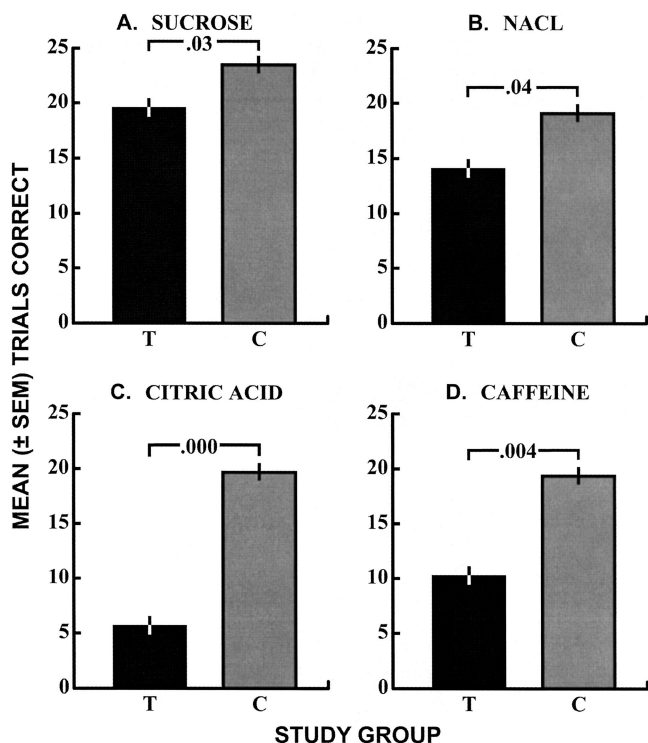


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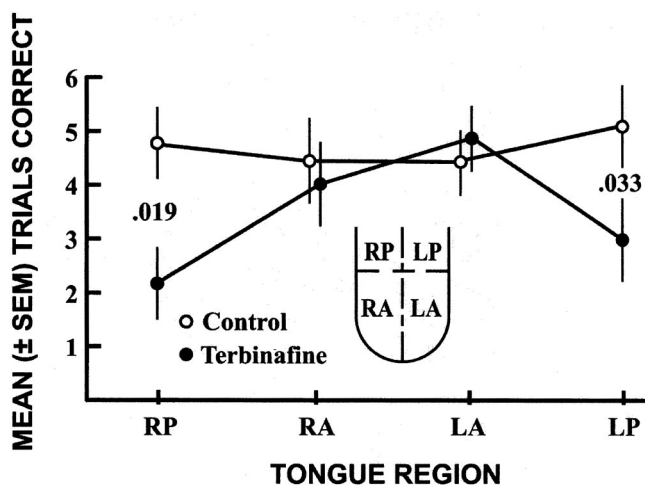


Fig. 2. A tongue region by group interaction approached significance for NaCl ($P = .07$), reflecting poorer performance on the posterior (CN IX) regions of the tongue.

[2.0]; $P = .40$), implying the dysfunction is confined to the taste system proper.

DISCUSSION

This study is the first to objectively verify the subjective chemosensory complaints of patients who have taken terbinafine. The findings are seemingly in accord with an earlier case report suggesting that sweet sensation was maintained longer than sour or bitter sensation in the progression of terbinafine-related dysfunction.⁸ Unlike another study examining taste thresholds in a single patient,⁵ however, marked terbinafine-related taste dysfunction was found. Conceivably, this reflects our use of a more sensitive measure of taste function than a whole-mouth threshold test. Alternatively, terbinafine may only affect taste quality. It is also possible that their subject, while noticing a problem, had only minor dysfunction at the time of testing because 1) she was younger (40 years) than all subjects of the present study (age is a significant risk factor for such disturbance),³ 2) terbinafine treatment was discontinued prematurely, and 3) some time elapsed between drug cessation and initial testing.

The physiologic mechanisms responsible for the terbinafine-induced loss of taste function remain unknown. Because terbinafine is highly lipophilic, the reported association between lower body mass index (BMI) and greater risk for terbinafine-related taste loss could reflect higher drug levels at the site of injury.³ As with the other allylamines, terbinafine inhibits ergosterol biosynthesis by way of inhibition of squalene epoxidase (SE, also known as squalene monooxygenase).⁹ SE is part of the fungal sterol synthesis pathway that creates the sterols needed for the fungal cell membrane. Because SE also catalyzes the second and likely rate-limiting step in cholesterol biosynthesis from farnesyl pyrophosphate and because cholesterol-reducing drugs such as atorvastatin (Lipitor) induce disturbances in taste function in humans,¹⁰ it is conceivable that terbinafine alters the cell

structure or function of taste-related neurons by way of the cholesterol pathway.

Support for the idea that terbinafine's effects occur at the level of the taste receptors or within the afferent gustatory pathway comes from the observation of relatively greater alteration in bitter and sour than in salty and sweet perception. Electrophysiologic studies in non-human primates suggest that, in the chorda tympani nerve, more sucrose-best and NaCl-best fibers are present than citric acid-best and caffeine-best fibers.¹¹ Assuming a similar situation in humans, it may be that the fewer fibers or receptors dedicated to a given taste sensation, the larger the adverse effects of terbinafine on their function.

Given the prevalence and magnitude of the adverse effects of terbinafine on taste function and the fact that that self-report markedly underestimates most chemosensory deficits, terbinafine likely induces taste dysfunction in many more persons than previously believed. Because being over the age of 65 years of age and having BMI less than 21 kg m⁻² are apparent risk factors for terbinafine-induced taste loss,³ physicians should be particularly on the alert for taste dysfunction in elderly persons taking this medication who may become depressed or alter their food intake in response to decreased taste sensation.

CONCLUSIONS

This study 1) empirically substantiates anecdotal case reports of taste loss after terbinafine usage, 2) demonstrates that all four major taste qualities are affected, and 3) suggests that olfactory dysfunction is not involved. Because self-report markedly underestimates chemosensory deficits, more extensive quantitative testing of patients receiving terbinafine will likely reveal a much higher prevalence of terbinafine-induced taste loss than currently reported.

Acknowledgments

The authors thank Dr. J. Castello, a Center patient and podiatrist, who had personally experienced terbinafine-related taste loss, for encouraging us to go forward with this project.

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