An Open-Label Controlled Trial of Theophylline for Treatment of Patients With Hyposmia

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Abstract: *Background:* To test the hypothesis that theophylline is effective in correcting smell loss in patients with hyposmia. *Methods:* Three hundred twelve patients with smell loss (hyposmia) were evaluated to determine characteristics of their loss by psychophysical measurements of detection and recognition thresholds, magnitude estimation and hedonic values for 4 odors (pyridine, nitrobenzene, thiophene, and amyl acetate) by use of a forced-choice 3-stimuli staircase design previously documented in a double-blind study. Patients were then treated in a fixed design open-label clinical trial with oral theophylline. Drug was given in equal divided doses from 200 to 800 mg daily for 2- to 8-month periods and subjective and psychophysical measurements of smell function and blood theophylline levels were measured; results were compared with those obtained before treatment. *Results:* Subjective smell loss improved in 157 (50.3%) patients; smell function was considered normal by 34 (21.7%). Overall, 10.9% of patients in the study considered smell function returned to normal. However, measurements of mean detection and recognition thresholds improved significantly at each drug level; measurements of mean magnitude estimation and hedonic also improved. Improvement was greater at drug doses of 600 and 800 mg than at 200 or 400 mg. Once improvement occurred, as long as treatment was maintained, it persisted for as long as follow-up was measured. *Conclusion:* Theophylline was effective in improving smell function in patients with smell loss. Improvement persisted as long as treatment was continued, which extended from 6 to 72 months.

Key Indexing Terms: Hyposmia; Theophylline; Phosphodiesterase inhibitors; Smell loss, Cyclic nucleotides. **[Am J Med Sci 2009;337(6):396–406.]**

Patients with smell loss (hyposmia) reflect a clinically diverse group of patients.[1–10] Although there is common agreement that many patients exhibit this clinical problem, there is no agreement with respect to their treatment. Indeed, most groups who evaluate these patients consider that there are few, if any, medically relevant treatments for them.

We have evaluated and treated patients with hyposmia for many years.[1,2] Initially, we attempted to define a biochemical molecular basis of the etiology(ies) of this diverse patient group because this is a chemosensory system that is influenced by body metabolism.[1,2,11–13] In an attempt to define the biochemistry of this system, we performed a total protein fractionation of saliva[14,15] and nasal mucus[16] because these fluids bathe both taste buds and olfactory epithelial tissues, respectively, and contain substances that are critical to maintain these sense organs.[14–16] On the basis of these studies, we initially discovered that some patients with smell loss had diminished salivary[17] and nasal mucus[18] levels of the saliva and nasal mucus protein carbonic anhydrase (CA) VI, a putative stem cell growth factor; treatment of these patients with exogenous zinc, which increased both salivary and nasal mucus CA VI,[19] corrected their smell loss.[19] However, these CA VI–deficient patients represent only a fraction of the total patient group.[1,2]

In an effort to define more fully the pathology of hyposmia, we investigated other potential biochemical molecular causes of smell and taste loss. In so doing, we recognized,[20,21] as others did before,[22–25] that cyclic nucleotides are present in saliva. We[20,21] and others before[26–30] considered these substances to play a role in both taste[20,26] and smell.[27–30] To study the potential biochemical molecular relationships between loss of smell and these cyclic nucleotides, we measured cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) in both saliva[31] and nasal mucus[32] in a large group of patients who complained of loss of smell. We found many of these patients exhibited lower than normal levels of both cAMP and cGMP in their saliva[31] and nasal mucus.[32] Because we had previously categorized severity of smell loss in these patients into 4 types,[2,33] we compared each type with quantitative measurements of cAMP and cGMP in their saliva (Henkin and Velicu, unpublished observations, 2008) and in their nasal mucus.[34] Results indicated that as smell loss severity increased (worsened) the levels of these cyclic nucleotides in saliva (Henkin and Velicu, unpublished observations, 2008) and nasal mucus[34] decreased. Because these cyclic nucleotides act as growth factors for several neural tissues,[35–37] including olfactory tissues,[27,28,38–42] we wondered whether these lower than normal levels of cyclic nucleotides played a role in generation of their hyposmia. To test this hypothesis, we treated a group of these patients with the phosphodiesterase (PDE) inhibitor theophylline to increase both saliva and nasal mucus levels of these cyclic nucleotides. We found in preliminary studies that hyposmia was corrected in many of them[1,2,43–45]; hyposmia correction was demonstrated by improvement of psychophysical measurements of hyposmia,[1,2,46] by increased brain activation to several olfactory stimuli through measurements of functional magnetic resonance imaging,[45] and with associated changes in serum theophylline.[42]

To confirm these initial studies, we initiated a more systematic study of theophylline treatment in patients with hyposmia. Theophylline was given to 312 patients in a fixed design controlled open trial over a period of 7 years. Results indicated that theophylline was useful in improving hyposmia in these patients.

METHODS

All studies were performed at The Taste and Smell Clinic, Washington, DC between June 2000 and February 2007 and constitute studies on consecutive patients who presented to the clinic because of loss of smell function and who exhibited salivary[32] and nasal mucus[33] levels of cAMP and cGMP below

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the normal mean. Studies were approved by the institutional review board of the Georgetown University Medical Center; all patients gave informed consent to participate in this study.

There were 312 patients aged 18 to 86 years [55 ± 1year, mean ± standard error mean (SEM)] in the study; they consisted of 178 women, aged 18 to 85 years (55 ± 2 years) and 134 men, aged 23 to 86 years (54 ± 3 years). Patients reported a history of smell loss extending from 2 months to 40 years (6.5 + 1.0 years). Etiology of smell loss varied; the major causes of hyposmia were postinfluenza-like hyposmia [97 patients, 31.1% of the total[47] (61 women, age 15–75 years, 54 ± 2 years; 36 men, age 34–75 years, 53 ± 2 years)], allergic rhinitis [97 patients, 31.1% of the total[48] (45 women, age 28–83 years, 57 ± 2 years; 52 men, aged 34–87 years, 57 ± 2 years)] followed by head injury [42 patients, 13.5%[49] (25 women, aged 18–80 years, 50 ± 4 years; 18 men, 18–73 years, 45 ± 4 years)], and several other causes, as previously described [76 patients, 24.4%[1,2] (33 women, 7–80 years, 55 ± 7 years; 43 men, age 15–61 years, 63 ± 3 years)]. Levels of CA VI in their saliva and nasal mucus were within normal levels.

Patients initially reported their sensory dysfunction as either loss of taste (ie, flavor) and/or smell function. This subjective response was documented by psychophysical measurements of olfactory function administered to each patient by use of a forced-choice, 3-stimuli, stepwise-staircase technique in a fixed, controlled design.[1,50] Efficacy of this technique and results of testing were previously documented in a double-blind clinical trial.[50] Four odors were used; they were pyridine (dead-fish odor), nitrobenzene (bitter-almond odor), thiophene (petroleum-like odor), and amyl acetate (banana-oil odor). Detection thresholds (DT), recognition thresholds (RT), and magnitude estimation (ME) values for each odor were determined as previously described.[1,50] Thresholds were converted into bottle units as previously described[50] and results reported as mean ± SEM of correct responses for each odor for each treatment group. ME was reported in % and reflect the means for all correct responses using data for the 4 highest odor concentrations presented (from 10^{-2} M—an absolute concentration). Mean ± SEM for ME for these correct responses for each odor for each treatment group was calculated.

Hedonic (H) value of each odor was also graded in %. H values were reported for all correct recognition responses using data for the same odor concentrations as used for ME (from 10^{-2} M—an absolute concentration using a −100–0–+100 scale). However, an arithmetic mean of responses was calculated for H based on the hedonic quality of the odor reported by the patient. Thus, if a patient considered the odor pleasant ("I wish to smell the odor again") the odor was graded as +1–+100 with respect to pleasantness; if the odor was considered unpleasant ("I do not wish to smell the odor again") the odor was graded as −1–−100 with respect to unpleasantness; if the odor was not considered either pleasant or unpleasant the odor was graded as neutral or 0. Results were obtained by calculating the arithmetical sum of each correct recognition response for each odor with respect to pleasantness, unpleasantness or neutrality. Mean ± SEM were obtained for each treatment group for each odor presented.

Independently, patients were also required daily to grade their ability to smell on a scale from 0 to 100, with 0 reflecting no overall smell function, 100 reflecting normal overall smell function and numbers between 0 and 100 reflecting estimation of whatever overall ability to smell odors was present.

Based on results of DT, RT, and ME, patients were initially classified with respect to severity of smell loss into 4 types (Table 1).[1,2] Patients with *anosmia* had the greatest severity of smell loss; they could neither detect nor recognize any vapor; ie, DT, RT, and ME were zero because they could not detect, recognize, or grade intensity of any odor, including an absolute concentration of any odorant (Table 1). No patients with anosmia were present in the study because of relative rarity of this condition.[1] Patients with *type I hyposmia* (96 patients) could detect some odors but could not recognize any odor correctly; thus, DTs for some odors were present but RTs and MEs for all odors were zero because they could neither recognize correctly nor thereby grade correctly intensity of any odor (Table 1). Patients with *type II hyposmia* (208 patients) could detect and recognize some odors but at levels greater than normal; thus, DTs and RTs were present but elevated above normal and MEs were present but at levels lower than normal (Table 1). Patients with *type III hyposmia* (8 patients) could detect and recognize all odors at normal levels (ie, normal DT and RT) but ME values for 1 or more odors were significantly decreased below normal (Table 1). Severity of smell loss graded from most to least severe loss was typed as anosmia > hyposmia type I > type II > type III and verified by demonstrating that as smell loss severity increased levels of nasal mucus cAMP and cGMP decreased.[32]

TABLE 1. Classification of smell loss

	Detection threshold DT in M/L	Recognition threshold RT in M/L	Magnitude estimation mean ME in %
Normals	+	+*	≥48
Patients			
Anosmia∞	0	0	0
Hyposmia			
Type I	±	0	0
Type II	±	±*	<48

+ Normal ($\leq 10^{-5}$ M for all odorants).
+* Normal ($\leq 10^{-2}$ M for all odorants) 0 Absent response.
± Present but < normal ($>10^{-5}$ M $<\infty$ for all odorants).
±* Present but < normal ($>10^{-2}$ M $<\infty$ for all odorants).
∞Inability to detect, recognize or judge intensity of an absolute concentration of odorant.

After determination of hyposmia patients were treated in an open-label fixed design controlled open trial. Patients were given an oral extended release theophylline in divided daily doses taken in the middle of breakfast and lunch. All patients were initially given 200 mg of theophylline; changes in this dose were administered based on subjective responses to therapy. If at a subsequent return visit on treatment patients reported ≥5% subjective improvement in overall smell function, they continued on this same dose of theophylline and were reevaluated after 4 to 6 months of continued treatment on this dose. Results from any subsequent return from these improved patients were not included in any subsequent data report (Figure 1). All subsequent comparisons between treated and untreated patients were made only between those patients continuing in the study compared with their own measurements obtained in the untreated state. If patients reported <5% subjective improvement their theophylline dose was increased by 200 mg daily and they returned to the clinic after 2 to 4 months and the same measurements used previously