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Improved Smell and Taste Dysfunction with Intranasal Theophylline

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Abstract

Purpose: There have been few studies which have demonstrated effective treatment of patients with smell loss (hyposmia). We have previously demonstrated improved hyposmia using oral theophylline in a long term study of a large patient group and using intranasal theophylline in a short term study in a small patient group. We now report hyposmic improvement with intranasal theophylline in a larger group of hyposmic patients for a more prolonged time period.

Methods: Ninety-four patients with hyposmia were initially studied at The Taste and Smell Clinic in Washington, DC before and after treatment with 20 µg of intranasal theophylline delivered twice into each nostril once daily for two months to 12 months. Subjective responses, olfactometry and gustometry were obtained before and after treatment.

Results: Subjective improvement in smell, flavor and taste function improved in 65% to 80% of patients with initial improvement occurring after two-four months of treatment with greater improvement occurring as treatment continued. Olfactometry results demonstrated significant improvement in smell function with threshold measurements in improved patients after 5 months to 8 months or 9 months to 12 months of treatment approximately two orders of magnitude lower (more sensitive) than their results prior to treatment.

Conclusion: Daily use of intranasal theophylline improved smell, taste and flavor perception subjectively. Results of olfactometry demonstrate that smell function improved significantly. There were no systemic side effects with intranasal theophylline treatment.

Keywords: Hyposmia; Hypogeusia; Theophylline; Smell loss; Taste loss; Flavor loss

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Introduction

Smell dysfunction is a common complaint related to many disorders [1-3]. We evaluated and treated many of these patients for several years with several medical therapies including oral theophylline [4-7]. This latter therapy improved smell dysfunction in many of these patients as demonstrated by improved olfactometry activity and by use of functional Magnetic Resonance Imagining of brain (fMRI) [4,7,8]. However, effectiveness of oral theophylline was dose dependant requiring 200 mg to 800 mg of the drug for periods of 4 to 18 months before efficacy was achieved; oral therapy was also limited due to its side effects (e.g., sleep disturbance, gastrointestinal upset, tachycardia, anxiety, etc.) and interactions with other medications [4,7]. Oral drug efficacy was associated with drug presence in several biological tissues as indicated by measurements of theophylline in nasal mucus, blood plasma and saliva [4,9,10]. While these clinical results do not define mechanism(s) of drug action the presence of the drug in nasal mucus may reflect its action at the olfactory epithelium as a G protein coupled receptor agonist and as a growth factor stimulating stem cells in the olfactory epithelium [4,11,12].

Because of limitations of the side effects of oral theophylline administration and extended time periods of treatment to obtain efficacy, it seemed logical to deliver the drug to the olfactory epithelium in an effort to stimulate directly olfactory receptor stem cells. To do this we performed a pilot study of drug delivery with an intranasal spray directly into the nose into the region of the olfactory epithelium. By this technique intranasal theophylline at doses of 20 µg daily were delivered to each nostril [13]. This technique improved smell function in eight of the ten treated patients with efficacy reported two weeks to two months after treatment initiation; there were no side effects of this method of drug administration and blood theophylline levels were undetectable. As previously noted oral theophylline required 200 mg to 800 mg daily [4,7] and 4 months to 12 months of

Table 1: Subjective changes after intranasal theophylline in all patients with hyposmia.

Period	Taste		Flavor		Smell	
	Change (%)	Number Improved (%)	Change (%)	Number Improved (%)	Change (%)	Number Improved (%)
2-4 months (89)	+9 ± 2*	58 [65]	+7 ± 2	58 [65]	+6 ± 2	58 [65]
5-8 months (77)	+15 ± 2	53 [69]	+12 ± 2	53 [69]	+11 ± 2	53 [69]
9-12 months (56)	+19 ± 3	45 [80]	+17 ± 3	45 [80]	+15 ± 4	45 [80]

*Mean ± SEM (in % change from pretreatment in all patients); see methods for details of percent changes
( ): total patient number; [ ]: number improved (%)

treatment to achieve this same effect.

To confirm the preliminary results of the pilot study we performed an open-label controlled clinical trial of intranasal theophylline in a larger, more diverse group of patients to evaluate drug efficacy, safety and time to obtain these effects [4].

Materials and Methods

Patients

Ninety-four patients [(41women, 53 men, aged 18 years to 85 years, 60 ± 2 years) (mean ± SEM)] presented to The Taste and Smell Clinic for evaluation and treatment of smell dysfunction. These patients were all patients who agreed to participate in this study with each patient signing a written agreement to perform the study which was approved by an established Institutional Review Board (Chesapeake IRB, Columbia, MD). Patients experienced dysfunction for periods of 2 months to 780 months (77 ± 13 months) prior to their first visit to The Clinic with 56% seeking treatment greater than one year after initiation of dysfunction. Clinical history was consistent with several etiologies of smell dysfunction: post-influenza-like illness (PIHH) (29 patients), allergic rhinitis (31 patients), head injury (13 patients), congenital loss of smell (5 patients) and various other causes (16 patients) [4,15-17]. Physical examination of the head and neck was within normal limits in each patient. Computed tomography scans and/or magnetic resonance imaging studies of brain did not exhibit pathology in the olfactory region and olfactory bulbs were present in each patient in whom these structures were evaluated.

Methods

Smell, taste and flavor perception were evaluated in each patient using subjective responses and standard specific tests of olfactometry and gustometry before treatment and at intervals of two- twelve months after therapy initiation [4].

Subjective responses consisted of subjective statements of the presence or absence of smell, taste and flavor perception using a scale from 0 to 100 with 0 indicating the absence of smell, taste or flavor and 100 indicating normal sensory function for each modality with values in between indicating partial presence of each sensory function [4]. Distortion of taste, flavor and smell perception were evaluated on a reversed scale of 100 to 0 with 100 now indicating the most distorted sensation ever experienced, zero indicating no distortions and values in between partial distortion presence. Subjective responses were obtained prior to olfactometry and gustometry testing by independent patient completion of written forms independent of the knowledge of cause or treatment condition of any patient in the study by any investigator. This scale or score appears at first glance to be linear. However, the apparent linear scale more appropriately reflects a psychophysical logarithmic scale with a 10% change in perception reported by patients reflecting one log unit in perceptual change. This is most easily understood by recognition of the multilog unit psychophysical constituency of both taste and smell perceptual sensory fields [18].

Intranasal theophylline was prepared by a contract pharmacy (Boothwyn Pharmacy, Upper Chichester, PA). Twenty μg of theophylline, in an aqueous solution containing small amounts of pharmacologically common excipients was delivered in a metered dose of 100 μL and inserted twice into each nostril once daily by use of a standard 15 mL plastic nasal spray dispenser (Madison Medical, Plattsburg, NY). Each fluid dose was maintained in the upper nasal airway without loss either in the pharyngeal region or out of the nasal cavity. Olfactometry was obtained by determination of Detection Thresholds (DT), Recognition Thresholds (RT), Magnitude Estimation (ME) and Hedonics (H) for four odorants: pyridine (pungent), nitrobenzene (bitter-almond), thiophene (petroleum-like) and amyl acetate (banana-like) [4]. By use of these tests measurements of receptor presence (DT), receptor/brain interaction (RT), receptor number (ME) and brain reactions to smell character (H) were determined.

Gustometry consisted of similar tests for quantitative measurement of taste function using four tastants: NaCl (salt), sucrose (sweet), HCl (sour) and urea (bitter) and determining DT, RT, ME and H as with olfactometry [4].

Patients treated with intranasal theophylline were evaluated at intervals of two months to 12 months in periods of two months to four months, five months to eight months and nine months to 12 months. At the end of each interval patients returned to the clinic and subjective responses were obtained by independent completion of the written forms on the 0 to 100 scale previously used for acuity and 100 to 0 for distortion. After completion of this form, tests of olfactometry or gustometry were then performed as they were at baseline without any knowledge of prior results. After completion of these tests a history was taken to confirm the presence of any changes in sensory function independent of any knowledge of the previously performed tests.

Subjective responses and results of olfactometry and gustometry were calculated after each patient returned to The Clinic. All results were obtained independent of any knowledge of pathology or prior treatment condition. Results were collated after 12 months of treatment and compared to results obtained at baseline and the termination of each treatment period. Paired responses were

Table 2: Subjective changes after intranasal theophylline only in patients with hyposmia who improved.

Period	Taste	Flavor	Smell
	Change (%)	Change (%)	Change (%)
2-4 months (58)	+16 ± 3*	+14 ± 2	+12 ± 2
5-8 months (53)	+21 ± 3	+18 ± 3	+16 ± 3
9-12 months (45)	+24 ± 4	+21 ± 4	+19 ± 3

*Mean ± SEM (in % change from pretreatment); see methods for details of percent changes

( ): total patient number

Table 3: Subjective changes after intranasal theophylline in all hyposmic patients categorized by diagnosis.

PIHH						
Period	Taste		Flavor		Smell	
	Change (%)	Number Improved (%)	Change (%)	Number Improved (%)	Change (%)	Number Improved (%)
2-4 months (28)	+4 ± 4*	18 [64]	+3 ± 3	18 [64]	+3 ± 2	18 [64]
5-8 months (22)	+14 ± 4	22 [100]	+11 ± 3	22 [100]	+10 ± 3	22 [100]
9-12 months (15)	+24 ± 7	13 [87]	+26 ± 7	13 [87]	+21 ± 7	13 [87]
Allergic Rhinitis						
Period	Taste		Flavor		Smell	
	Change (%)	Number Improved (%)	Change (%)	Number Improved (%)	Change (%)	Number Improved (%)
2-4 months (29)	+13 ± 4	17 [59]	+7 ± 5	17 [59]	+7 ± 5	17 [59]
5-8 months (24)	+18 ± 5	15 [63]	+15 ± 5	15 [63]	+14 ± 5	15 [63]
9-12 months (17)	+17 ± 6	13 [76]	+10 ± 4	13 [76]	+16 ± 6	13 [76]
Head Injury						
Period	Taste		Flavor		Smell	
	Change (%)	Number Improved (%)	Change (%)	Number Improved (%)	Change (%)	Number Improved (%)
2-4 months (12)	+23 ± 7	11 [92]	+19 ± 7	11 [92]	+9 ± 4	11 [92]
5-8 months (13)	+19 ± 6	10 [77]	+14 ± 6	10 [77]	+5 ± 2	10 [77]
9-12 months (10)	+27 ± 9	9 [90]	+23 ± 8	9 [90]	+8 ± 2	9 [90]
Congenital						
Period	Taste		Flavor		Smell	
	Change (%)	Number Improved (%)	Change (%)	Number Improved (%)	Change (%)	Number Improved (%)
2-4 months (4)	0 ± 0	0 [0]	0 ± 0	0[0]	+1 ± 1	1 [25]
5-8 months (4)	0 ± 0	0 [0]	0 ± 0	0[0]	+3 ± 2	2 [50]
9-12 months (4)	+5 ± 5	[75]	0 ± 0	0[0]	+6 ± 5	3 [75]
Idiopathic						
Period	Taste		Flavor		Smell	
	Change (%)	Number Improved (%)	Change (%)	Number Improved (%)	Change (%)	Number Improved (%)
2-4 months (8)	+7 ± 6	5 [62]	+3 ± 5	5 [62]	+10 ± 5	5 [62]
5-8 months (8)	+6 ± 5	5 [62]	+8 ± 6	5 [62]	+12 ± 6	5 [62]
9-12 months (5)	+17 ± 11	4 [80]	+16 ± 7	4 [80]	+19 ± 9	4 [80]
Other						
Period	PIHH	Taste		Flavor		Smell	
		Change (%)	Number Improved (%)	Change (%)	Number Improved (%)	Change (%)	Number Improved (%)
2-4 months	(8)	0 ± 0	6 [75]	+3 ± 2	6 [75]	+8 ± 7	6 [75]
5-8 months	(6)	+15 ± 4	5 [83]	+14 ± 11	5 [83]	+12 ± 5	5 [83]
9-12 months	(5)	+8 ± 4	5 [100]	+24 ± 17	5 [100]	+14 ± 8	5 [100]

*Mean ± SEM (in % change from pretreatment in all patients); see methods for details of percent changes
( ): total patient number; [ ]: number improved (%)

compared before and after treatment with significance of differences established by Student's t-test with $p<0.05$ considered significant.

Results

Subjective responses

Subjective perception of smell and flavor function prior to treatment was considered to be 0 by each patient and in those with distortions considered to be 100. Smell and flavor perception improved as treatment proceeded with 65% of all patients (58 of 89) reporting improvement at 2 months to 4 months of treatment, 69% (53 of 77) reporting improvement after 5 months to 8 months and 80% (45 of 56) reporting improvement after 9 months to 12 months (Table 1).

Distortions diminished in intensity among improved patients but did not do so among non improved patients. With respect to all patients smell acuity subjectively improved by 6% to 14%, flavor by 6% to 18% and taste by 9% to 20% (Table 1). As treatment preceded each sensory acuity parameter improved, whereas each distortion parameter diminished (data not shown). Among patients who improved on treatment overall improvement in taste, flavor and smell combined was 46% (Table 2).

Average improvement (in percent) for each sensory parameter among patients who reported improvement varied from 1% to 100% with a mean improvement among all treated patients (improved or not) varying from 6% to 15% for smell function, from 9% to 19%

Table 4: Gustometry and olfactometry pre and post intranasal theophylline treatment in all hyposmic patients.

		Taste (mM/L)				Smell (M/L)			
Period	**Condition**	**NaCl**	**Sucrose**	**HCl**	**Urea**	**Prydine**	**NO_2B**	**Thio**	**AA**
2-4 months	**DT**								
	Pre	4.73 ± 0.19*	4.24 ± 0.19	4.53 ± 0.17	4.79 ± 0.25	7.26 ± 0.33	7.65 ± 0.39	7.35 ± 0.41	7.42 ± 0.41
	Post	4.45 ± 0.19	3.94 ± 0.17	3.89 ± 0.17	4.34 ± 0.24	6.24 ± 0.37	6.47 ± 0.42	6.03 ± 0.43	6.42 ± 0.43
	P	0.3	0.25	0.01	0.19	0.04	0.04	0.03	0.09
	RT								
	Pre	4.97 ± 0.21*	4.34 ± 0.19	4.72 ± 0.17	4.97 ± 0.26	8.17 ± 0.33	8.40 ± 0.40	7.80 ± 0.42	8.49 ± 0.40
	Post	4.62 ± 0.19	4.01 ± 0.17	4.11 ± 0.17	4.39 ± 0.24	7.07 ± 0.37	7.04 ± 0.43	6.54 ± 0.44	7.07 ± 0.43
	P	0.22	0.2	0.01	0.11	0.03	0.02	0.04	0.02
	ME								
	Pre	46 ± 2*	40 ± 2	47 ± 2	40 ± 2	29 ± 3	12 ± 2	17 ± 2	12 ± 2
	Post	47 ± 2	42 ± 2	47 ± 2	44 ± 3	35 ± 3	20 ± 3	25 ± 3	20 ± 2
	P	0.58	0.6	0.99	0.23	0.11	0.01	0.03	0.001
	H								
	Pre	-18 ± 3	19 ± 3	-26 ± 3	-31 ± 3	-23 ± 3	1 ± 1	-11 ± 2	1 ± 1
	Post	-19 ± 3	17 ± 3	-30 ± 3	-36 ± 3	-30 ± 3	1 ± 2	-16 ± 3	3 ± 2
	P	0.8	0.59	0.33	0.22	0.1	0.9	0.14	0.57
5-8 months	**DT**								
	Pre	4.73 ± 0.22	4.25 ± 0.20	4.49 ± 0.19	4.90 ± 0.27	7.26 ± 0.36	7.78 ± 0.43	7.43 ± 0.45	7.55 ± 0.45
	Post	4.47 ± 0.20	3.84 ± 0.16	4.00 ± 0.18	4.16 ± 0.25	5.79 ± 0.43	6.13 ± 0.49	5.68 ± 0.47	5.77 ± 0.50
	P	0.38	0.12	0.06	0.05	0.01	0.01	0.01	0.01
	RT								
	Pre	4.96 ± 0.24	4.34 ± 0.20	4.71 ± 0.20	5.12 ± 0.29	8.31 ± 0.36	8.55 ± 0.43	7.92 ± 0.46	8.64 ± 0.44
	Post	4.66 ± 0.22	3.96 ± 0.15	4.14 ± 0.18	4.21 ± 0.25	6.32 ± 0.45	6.57 ± 0.50	6.27 ± 0.49	6.39 ± 0.49
	P	0.36	0.14	0.03	0.02	0.001	0.001	0.01	0.001
	ME								
	Pre	46 ± 2*	40 ± 2	46 ± 2	38 ± 3	27 ± 3	12 ± 2	16 ± 2	10 ± 2
	Post	50 ± 3	44 ± 3	48 ± 3	44 ± 3	33 ± 3	21 ± 3	25 ± 3	21 ± 3
	P	0.3	0.31	0.57	0.09	0.16	0.01	0.02	0.001
	H								
	Pre	-19 ± 3	20 ± 3	-27 ± 3	-30 ± 3	-21 ± 3	2 ± 1	-11 ± 2	1 ± 1
	Post	-24 ± 3	14 ± 4	-31 ± 4	-42 ± 7	-27 ± 3	3 ± 2	-16 ± 3	3 ± 2
	P	0.23	0.32	0.4	0.13	0.22	0.57	0.16	0.67
9-12 months	**DT**								
	Pre	4.82 ± 0.27	4.29 ± 0.26	4.65 ± 0.23	4.96 ± 0.30	7.22 ± 0.45	7.67 ± 0.52	7.33 ± 0.53	7.45 ± 0.54
	Post	4.29 ± 0.28	3.87 ± 0.24	4.07 ± 0.22	4.22 ± 0.30	5.76 ± 0.53	5.65 ± 0.57	5.64 ± 0.58	5.60 ± 0.58
	P	0.18	0.23	0.07	0.1	0.04	0.01	0.03	0.02
	RT								
	Pre	5.13 ± 0.32	4.29 ± 0.26	4.85 ± 0.23	5.13 ± 0.33	8.13 ± 0.45	8.42 ± 0.52	7.85 ± 0.54	8.49 ± 0.55
	Post	4.35 ± 0.27	3.96 ± 0.23	4.18 ± 0.23	4.22 ± 0.30	5.98 ± 0.56	6.29 ± 0.57	5.95 ± 0.61	6.31 ± 0.58
	P	0.06	0.35	0.04	0.05	0.001	0.01	0.02	0.01
	ME								
	Pre	45 ± 3*	39 ± 3	45 ± 2	36 ± 3	28 ± 4	15 ± 3	18 ± 3	12 ± 2
	Post	49 ± 3	38 ± 3	42 ± 3	41 ± 3	35 ± 4	23 ± 3	27 ± 4	25 ± 4
	P	0.34	0.84	0.5	0.25	0.2	0.05	0.08	0.01
	H								
	Pre	-16 ± 3	22 ± 4	-23 ± 4	-27 ± 3	-21 ± 4	-1 ± 2	-13 ± 3	-1 ± 2
	Post	-25 ± 4	17 ± 4	-27 ± 3	-32 ± 4	-28 ± 4	-2 ± 3	-19 ± 4	-3 ± 3
	P	0.06	0.42	0.48	0.36	0.19	0.75	0.25	0.4

*Mean ± SEM in bottle units (4) [x] Mean ± SEM in % (4); DT: detection thresholds; RT: recognition thresholds; ME: magnitude estimation; H: hedonics; Thio: thiophene (petroleum-like odor); AA: amyl acetate (banana-oil odor) NaCl (salt); Sucrose (sweet); HCl (sour); Urea (bitter); Prydine (dead-fish odor); NO2B: nitrobenzene (bitter-almond odor); P: Significance of changes with respect to pretreatment; N: 89 patients at 2-4 months, 77 patients at 5-8 months, 56 patients at 9-12 months

Table 5: Changes in olfactometry in hyposmic patients who reported improvement or no improvement in smell responses after intranasal theophylline.

PYRIDINE								
Treatment Period	**Detection Thresholds**		**Recognition Thresholds**		**Magnitude Estimation**		**Hedonics**	
2- 4 months	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Improved (58)	6.74 ± 0.40*	5.36 ± 0.43[a] [20]	7.67 ± 0.38	6.19 ± 0.43[a] [19]	33 ± 4*	42 ± 4b [27]	-29 ± 4	-37 ± 4[c] [28]
Not improved (31)	8.13 ± 0.53	7.87 ± 0.58 [.04]	8.97 ± 0.56	8.71 ± 0.58 [.02]	22 ± 4	23 ± 4 [5]	-14 ± 4	-17 ± 3 [21]
5-8 month								
Improved (53)	6.79 ± 0.43	4.94 ± 0.49[a] [26]	7.79 ± 0.41	5.49 ± 0.51[a] [31]	31 ± 3	40 ± 4[e] [25]	-27 ± 4	-32 ± 4 [18]
Not improved (24)	8.29 ± 0.57	8.04 ± 0.66 [.06]	9.46 ± 0.69	8.54 ± 0.76[.10]	18 ± 5	17 ± 4 [-5]	-9 ± 6	-14 ± 4 [-40]
9-12 month								
Improved (45)	6.93 ± 0.51	5.36 ± 0.58[a] [27]	7.76 ± 0.49	5.40 ± 0.59[a][33]	29 ± 4	37 ± 4 [30]	-24 ± 4	-29 ± 4 [17]
Not improved (11)	8.55 ± 0.79	7.73 ± 1.04 [.09]	9.73 ± 0.98	8.64 ± 1.11 [13]	25 ± 10	27 ± 8 [-4]	-9 ± 12	-25 ± 8 [20]
NITROBENZENE								
Treatment Period	**Detection Thresholds**		**Recognition Thresholds**		**Magnitude Estimation**		**Hedonics**	
2-4 months	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Improved (58)	6.95 ± 0.48	5.45 ± 0.49[a] [21]	7.62 ± 0.49	6.02 ± 0.50[a] [22]	16 ± 3	27 ± 3[a] [68]	1 ± 2	-0.4 ± 3 [30]
Not improved (31)	8.71 ± 0.65	8.39 ± 0.66 [.04]	9.61 ± 0.62	8.97 ± 0.71 [.06]	6 ± 2	8 ± 3 [17]	3 ± 1	3 ± 2 [0]
5-8 month								
Improved (53)	7.09 ± 0.51	5.08 ± 0.54[a] [28]	7.96 ± 0.51	5.62 ± 0.55[a] [29]	14 ± 2	27 ± 4[a] [80]	2 ± 2	4 ± 4 [100]
Not improved(24)	9.29 ± 0.75	8.63 ± 0.82 [.07]	9.83 ± 0.75	8.83 ± 0.87 [1.0]	6 ± 2	7 ± 3 [0]	1 ± 1	2 ± 2 [50]
9-12 month								
Improved (45)	7.31 ± 0.56	5.09 ± 0.58[a] [31]	8.07 ± 0.58	5.80 ± 0.62[a] [27]	16 ± 3	25 ± 4[e] [65]	-0.2 ± 2	-4 ± 4 [110]
Not improved (11)	9.55 ± 1.12	8.45 ± 1.21 [.07]	10.18 ± 1.03	8.82 ± 1.19 [.07]	10 ± 5	14 ± 6 [27]	-3 ± 3	6 ± 3 [15]
THIOPHENE								
Treatment Period	**Detection Thresholds**		**Recognition Thresholds**		**Magnitude Estimation**		**Hedonics**	
2- 4 months	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Improved (58)	6.55 ± 0.51	4.84 ± 0.48[a] [26]	7.02 ± 0.50	5.33 ± 0.51[a] [24]	23 ± 3	32 ± 3[d] [45]	-15 ± 3	-21 ± 4 [40]
Not improved (31)	8.61 ± 0.65	8.26 ± 0.68 [.05]	9.03 ± 0.71	8.81 ± 0.68 [-2]	8 ± 2	12 ± 3 [50]	-4 ± 1	-7 ± 3 [-75]
5-8 month								
Improved (53)	6.85 ± 0.53	4.51 ± 0.51[a] [33]	7.28 ± 0.54	5.09 ± 0.53[a] [30]	21 ± 3	32 ± 4[b] [45]	-15 ± 3	-21 ± 4 [31]
Not improved (24)	8.71 ± 0.76	8.42 ± 0.73 [-.06]	9.33 ± 0.82	9.04 ± 0.77 [-3]	4 ± 1	8 ± 3[d] [25]	-2 ± 1	-5 ± 2 [-200]
9-12 month								
Improved (45)	6.87 ± 0.58	5.09 ± 0.61[b] [39]	7.40 ± 0.60	5.27 ± 0.64[a] [28]	21 ± 4	32 ± 5[e] [57]	-15 ± 4	-22 ± 5 [57]
Not improved (11)	9.55 ± 0.99	7.91 ± 1.30 [-14]	10.00 ± 1.03	8.73 ± 1.28 [-3]	8 ± 3	10 ± 4 [0]	-4 ± 3	-4 ± 2 [-38]
AMYL ACETATE								
Treatment Period	**Detection Thresholds**		**Recognition Thresholds**		**Magnitude Estimation**		**Hedonics**	
2- 4 months	**Pre**	**Post**	**Pre**		**Pre**	**Post**	**Pre**	**Post**
Improved (58)	6.78 ± 0.49	5.48 ± 0.51[a][19]	7.83 ± 0.50	6.16 ± 0.49[a] [21]	15 ± 2	26 ± 3[a] [86]	-0.4 ± 2	4 ± 3 [90]
Not improved(31)	8.39 ± 0.71	8.16 ± 0.68 [-4]	9.52 ± 0.61	8.77 ± 0.72 [-2]	6 ± 2	9 ± 2 [50]	2 ± 1	1 ± 1 [-50]
5-8 month								
Improved (53)	7.04 ± 0.54	4.58 ± 0.53[a] [35]	8.26 ± 0.54	5.25 ± 0.54[a] [35]	12 ± 2	26 ± 4[a] [108]	1 ± 2	2 ± 3 [0]
Not improved (24)	8.67 ± 0.80	8.50 ± 0.83 [-3]	9.46 ± 0.75	9.04 ± 0.80 [-10]	5 ± 2	10 ± 3 [100]	2 ± 1	4 ± 3 [0]
9-12 month								
Improved (45)	7.11 ± 0.60	5.04 ± 0.62[a] [31]	8.11 ± 0.61	5.73 ± 0.61[a] [33]	14 ± 3	27 ± 4[b] [115]	-0.3 ± 3	-5 ± 3 [250]
Not improved (11)	9.27 ± 1.09	8.36 ± 1.32 [-4]	10.36 ± 1.00	9.09 ± 1.34 [-16]	6 ± 3	14 ± 6 [80]	2 ± 1	5 ± 4 [-39]

* Mean ± SEM in bottle units (4); X Mean ± SEM in % (4). With respect to before treatment

[a]p<0.001; [b]p<0.005; [c]p<0.01; [d]p<0.02; [e]p<0.05

( ): patient number; [ ]: percent change; †: mean; ±: SEM

Table 6: Changes in gastometry in hyposmic patients who reported improvement or no improvement in smell responses after intranasal theophylline.

NaCl								
Treatment Period	**Detection Threshold**		**Recognition Threshold**		**Magnitude Estimation**		**Hedonics**	
	Before	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**
2-4 months								
Improved (58)	4.83 ± 0.23	4.43 ± 0.24[e] [**.07**]	5.07 ± 0.25	4.67 ± 0.23[e] [**0**]	44 ± 3	48 ± 3[e] [**.09**]	-17 ± 3	-18 ± 4 [**.06**]
Not improved (31)	4.55 ± 0.32	4.48 ± 0.32 [**-.02**]	4.77 ± 0.40	4.52 ± 0.32 [**.06**]	48 ± 4	47 ± 5 [**-2**]	-20 ± 4	-21 ± 5 [**.09**]
5-8 months								
Improved (53)	4.74 ± 0.25	4.34 ± 0.23[d] [**.07**]	5.00 ± 0.27	4.58 ± 0.24[d] [**.07**]	47 ± 3	54 ± 3[b] [**.08**]	-21 ± 3	-26 ± 4 [**26**]
Not improved (24)	4.71 ± 0.42	4.75 ± 0.41 [**.01**]	4.88 ± 0.52	4.83 ± 0.47 [**.20**]	44 ± 5	41 ± 5 [**-13**]	-16 ± 4	-20 ± 5 [**18**]
9-12 months								
Improved (45)	4.60 ± 0.31	4.16 ± 0.29 [**.08**]	4.98 ± 0.37	4.24 ± 0.29[c] [**15**]	46 ± 3	52 ± 4[d] [**11**]	-18 ± 3	-29 ± 4[d] [**42**]
Not improved (11)	5.45 ± 0.59	4.64 ± 0.74 [**.05**]	5.45 ± 0.59	4.64 ± 0.74 [**15**]	43 ± 8	39 ± 8 [**-11**]	-12 ± 6	-15 ± 8 [**10**]
Sucrose								
Treatment Period	**Detection Threshold**		**Recognition Threshold**		**Magnitude Estimation**		**Hedonics**	
	Before	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**
2-4 months								
Improved (58)	4.40 ± 0.23	4.00 ± 0.21[b] [**.13**]	4.47 ± 0.23	4.07 ± 0.21[c] [**.08**]	39 ± 3	43 ± 3[e] [**10**]	21 ± 3	16 ± 5 [**24**]
Not improved (31)	3.94 ± 0.32	3.84 ± 0.30 [**.02**]	4.10 ± 0.32	3.91 ± 0.29 [**.04**]	41 ± 4	40 ± 4 [**0**]	15 ± 6	17 ± 5 [**3**]
5-8 months								
Improved (53)	4.25 ± 0.25	3.77 ± 0.19[c] [**.11**]	4.34 ± 0.26	3.92 ± 0.16[e] [**.09**]	41 ± 3	47 ± 3[b] [**14**]	21 ± 4	16 ± 5 [**23**]
Not improved (24)	4.25 ± 0.35	3.96 ± 0.33 [**-.05**]	4.33 ± 0.32	4.00 ± 0.32 [**.01**]	38 ± 4	38 ± 5 [**-.05**]	16 ± 6	10 ± 6 [**-41**]
9-12 months								
Improved (45)	4.13 ± 0.29	3.84 ± 0.28 [**.08**]	4.18 ± 0.29	3.89 ± 0.27 [**.25**]	40 ± 3	40 ± 3 [**24**]	20 ± 4	17 ± 4 [**10**]
Not improved (11)	4.91 ± 0.46	3.91 ± 0.37[e] [**0**]	4.91 ± 0.46	4.18 ± 0.40 [**.01**]	38 ± 5	32 ± 5 [**-.20**]	25 ± 7	13 ± 4[d] [**-19**]
HCl								
Treatment Period	**Detection Threshold**		**Recognition Threshold**		**Magnitude Estimation**		**Hedonics**	
	Before	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**
2-4 months								
Improved (58)	4.64 ± 0.21	3.97 ± 0.20[a] [**22**]	4.83 ± 0.21	4.17 ± 0.21[a] [**14**]	46 ± 2	48 ± 2 [**7**]	-24 ± 4	-31 ± 4 [**29**]
Not improved (31)	4.39 ± 0.27	3.74 ± 0.29[c] [**14**]	4.58 ± 0.30	4.00 ± 0.30 [**.09**]	48 ± 4	45 ± 4 [**-4**]	-28 ± 5	-29 ± 5 [**7**]
5-8 months								
Improved (53)	4.53 ± 0.23	4.04 ± 0.20[e] [**10**]	4.75 ± 0.23	4.25 ± 0.20[e] [**10**]	47 ± 3	51 ± 3 [**6**]	-29 ± 4	-36 ± 4 [**23**]
Not improved (24)	4.42 ± 0.32	3.88 ± 0.35 [**13**]	4.63 ± 0.35	3.88 ± 0.35[e] [**13**]	44 ± 4	43 ± 5 [**-7**]	-23 ± 5	-22 ± 7 [**-12**]
9-12 months								
Improved (45)	4.47 ± 0.26	4.09 ± 0.26 [**10**]	4.71 ± 0.27	4.16 ± 0.26[d] [**12**]	46 ± 3	44 ± 3 [**2**]	-23 ± 5	-28 ± 3 [**26**]
Not improved (11)	5.09 ± 0.51	3.91 ± 0.39[b] [**3**]	5.09 ± 0.51	4.18 ± 0.42[d] [**2**]	42 ± 6	36 ± 7 [**-18**]	-25 ± 6	-23 ± 7 [**-14**]
Urea								
Treatment Period	**Detection Threshold**		**Recognition Threshold**		**Magnitude Estimation**		**Hedonics**	
	Before	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**
2-4 months								
Improved (58)	5.07 ± 0.30	4.38 ± 0.30[d] [**13**]	5.17 ± 0.30	4.36 ± 0.28[b] [**15**]	37 ± 3	45 ± 3[a] [**21**]	-28 ± 3	-37 ± 3[d] [**31**]
Not improved (31)	4.42 ± 0.42	4.26 ± 0.40 [**3**]	4.74 ± 0.49	4.45 ± 0.44 [**5**]	42 ± 5	42 ± 5 [**-2**]	-36 ± 5	-34 ± 5 [**-3**]
5-8 months								
Improved (53)	4.98 ± 0.30	4.08 ± 0.27[b] [**18**]	5.11 ± 0.30	4.09 ± 0.27[a] [**19**]	38 ± 3	48 ± 4[a] [**26**]	-30 ± 4	-40 ± 4[d] [**32**]
Not improved (24)	4.71 ± 0.56	4.21 ± 0.56 [**6**]	5.13 ± 0.64	4.33 ± 0.54 [**19**]	37 ± 5	38 ± 6 [**0**]	-29 ± 5	-49 ± 23 [**-3**]
9-12 months								
Improved (45)	4.80 ± 0.33	4.27 ± 0.34 [**10**]	4.96 ± 0.34	4.27 ± 0.34[d] [**13**]	37 ± 3	43 ± 3[d] [**.7**]	-28 ± 4	-33 ± 4 [**23**]
Not improved (11)	5.55 ± 0.92	3.91 ± 0.61[e] [**0**]	5.73 ± 0.94	3.91 ± 0.61[e] [**0**]	35 ± 7	36 ± 8 [**0**]	-27 ± 7	-26 ± 9 [**-12**]

*Mean ± SEM in bottle units (4); [X] Mean ± SEM in % (4). With respect to before treatment
[a]p<0.001; [b]p<0.005; [c]p<0.01; [d]p<0.02; [e]p<0.05
( ): patient number; [ ]: percent change

for taste function and from 7% to 17% for flavor perception with improvement occurring as treatment time increased (Table 1). At 9 months to 12 months of treatment 14 of 37 patients (38%) who considered olfactory acuity improved, improved >50% whereas 6 of these patients (16%) considered olfactory acuity improved >80%. On the other hand, 35% (31 of 89) reported no improvement after 2

months to 4 months, 31% (24 of 77) reported no improvement after 5 months to 8 months and 20% (11 of 56) reported no improvement after 9 months to 12 months. Among patients who reported improvement on treatment overall improvement was 46% better (Table 2) than among all treated patients (Table 1).

While some patients in each pathological category reported improved smell, flavor and taste perception, the numbers in some categories were small. For example 13 of 15 patients (87%) with PIHH reported improvement in smell perception after 9 months to 12 months of treatment (Table 3). Among patients with head injuries nine of 10 patients (90%) reported improvement in smell function after 9 months to 12 months of treatment and three of four patients with congenital hyposmia reported some initiation of smell function (Table 3).

Olfactometry and gustometry

Tables 4-6 demonstrate gustometry and olfactometry in patients treated with intranasal theophylline after two months to 12 months of treatment. Mean smell perception for DT and RT improved significantly for all odorants in all patients after two-four months of treatment except for DT for amyl acetate (Table 4); this improvement persisted after five months to 12 months with DT for amyl acetate now significantly improved (Table 4). Similarly improvement in ME for all qualities except for pyridine also improved in the same manner. Mean taste perception improved in all patients but significantly only for DT and RT of HCl after 2 months to 4 months, DT and RT for urea after 5 months to 8 months and for RT for HCl and urea after 9 months to 12 months (Table 4). Results for flavor perception and smell, flavor, and taste distortions were obtained only by subjective response.

Table 5 illustrates olfactometry in hyposmic patients after two to 12 months of intranasal theophylline treatment among those who reported smell improvement and those who did not. For smell perception, mean DTs, RTs and MEs for all odorants improved significantly in the 58 of the 89 patients who reported subjective improvement (65%) after 2 months to 4 months of treatment whereas smell perception did not improve in 31 (35%) who did not report subjective improvement. In 21 of the 58 improved patients 36% had measured responses for olfactory DT, RT and ME for all odorants which returned to the normal range with results of DT and RT two SD below their pretreatment results. In patients who did not improve no significant changes in any smell parameter was measured. Improvement in DTs, RTs, and ME for all odorants progressed as treatment continued for 5 months to 8 months and 9 months to 12 months with 22 of 55 patients (40%) with olfactory DT, RT and ME for all odorants returning to normal range at 5 months to 8 months and 25 of 44 (57%) patients with DT, RT and ME for all odorants returning to the normal range after 9 months to 12 month. Significant changes did not occur in any smell parameter in any patient who subjectively stated that no improvement occurred.

Table 6 illustrates gustometry in patients with hyposmia who reported smell improvement and no smell improvement after two to 12 months of intranasal theophylline. Whereas all parameters of taste perception improved significant improvement was measured in patients who reported improved smell function only for RT and ME for NaCl, DT, RT and ME for sucrose, HCl and urea after two months to four months, for urea DT and ME after 5 months to 8 months and for RT for urea and HCl after 9 months to 12 months. Patients who reported no smell improvement demonstrated no significant change in taste function except for improved DT for sucrose after 9 months to 12 months of treatment.

Discussion

These results indicate that intranasal theophylline improves smell dysfunction in most hyposmic patients. Results are consistent with results of our previous pilot study in 10 hyposmic patients in whom smell perception improved significantly in eight with treatment with intranasal theophylline [13]. However, in the current study, patients were more numerous and more diverse in their underlying pathology and studies were more extensive in that measurements of changes of sensory perception were evaluated for periods of two months to 12 months. In this study, although not in our pilot study, we also included gustometry in which improved measurements in taste function occurred along with significant improvement in olfactometry (Tables 4-6).

As in our pilot study not all patients in this study reported subjective improvement in smell function or demonstrated improvement by olfactometry. Nevertheless improvement occurred subjectively in each pathological category of smell loss even when all patients were included in these measurements (Table 3).

Subjective improvement in smell, flavor and taste perception varied between 1% to 100% with progressive improvement as time continued (Table 1 and 2). Among all patients overall olfactory acuity was reported improved by 6% to 14% while among patients who reported overall improvement in smell function acuity improved by 12% to 18% (Table 1 and 2). These reported response ranges may be considered low since patients underestimated the degree of their improvement. Since patients initially stated that they could neither detect nor recognize any odor, similar to patients who considered themselves to be totally blind or deaf, this improvement after treatment indicated a significant subjective return of their ability to detect and recognize all odors from what they previously considered an "anosmic" state. Indeed this was demonstrated by olfactometry with DT, RT, and ME returning to the near normal range for all odorants in many patients.

Measurements of improved smell function was reported as early as 2 to 4 weeks of treatment and confirmed at the two to four month clinic visit. At this time 65% of treated patients reported smell improvement. With continued treatment more patients reported smell improvement with an increased percentage in olfactory acuity (Table 1 and 2). This timed phenomenon of change can be related to a two phase action of theophylline in improving smell function. Initially, with the absence of olfactory receptor activity the brain itself may "go to sleep". In the first phase of theophylline action theophylline may stimulate receptor and stem cell function with an improvement in smell detection. This is reflected in patients reporting an increased ability to detect but not necessarily recognize olfactory stimuli. However, over time as olfactory receptor activity increases, the second phase of smell improvement occurs in which brain activity improved. It comes into play with the return of smell recognition consistent with an increase in brain plasticity and an increase in percent change in smell acuity with the patient reporting improvement in olfactory recognition associated with the improved olfactory memory.

However, careful evaluation of initial olfactometry indicated that prior to treatment all patients could detect and/or recognize some odors albeit at levels far below normal levels. It was this significant subjective loss of smell and flavor that caused patients to consider their smell and flavor acuity as zero prior to their treatment although

all could detect and/or recognize odors at high levels of odorant.

Patients who subjectively improved smell perception with intranasal theophylline were more than reported improvement with oral theophylline (oral 5%, intranasal current study 12% to 18%) [7] (Table 1). Improvement with the intranasal drug occurred more rapidly than with oral theophylline and did not induce any systemic side effects. Indeed, this result was obtained with 80 µg of the intranasal drug daily as opposed to 200 mg to 800 mg daily for the oral drug. The only side effect of intranasal administration was occasional reports of transient nasal irritation in three patients. Blood theophylline levels were undetectable in any patient taking the intranasal drug.

Mechanism(s) for the action of intranasal theophylline in improving smell, taste and flavor perception is not clearly defined by these clinical data. However, on the basis of previous studies we suggest that this improvement in sensory perception is dependent upon theophylline action in several ways. By stimulating gustatory and olfactory stem cells secondary to increased secretion of nasal mucus and saliva growth factors such as cAMP, cGMP and sonic hedgehog, these results are consistent with theophylline allowing odorants and tastants to stimulate presynaptic G protein coupled receptors and other targets through the action of these moieties to stimulate neuronal excitability and synaptic transmission [19-21]. In addition, there are indications that direct drug introduction into the nose may not only act on olfactory stem cells in the olfactory epithelium but also could enter the brain bypassing the blood-brain barrier by direct entrance through the cribriform plate [12,22]. In this sense, intranasal theophylline could influence smell, taste and flavor perception through a direct action in the brain.

There are important limitations to this study. A total of 31 patients dropped out of this study. Patient number decreased over the test periods mainly due to financial considerations of patient inability to return to The Clinic in Washington, D.C at frequent intervals from their homes at a distance from The Clinic. Eighty-nine of the original 94 patients were studied after two to four months of treatment with five studied later after 5 months to 8 months of treatment. Fifteen patients dropped out after five months to eight months of treatment with four of the original 94 studied after 9 months to 12 months; of these 15, six reported improved smell and taste function. Seventeen patients dropped out after 9 months to 12 months of treatment with eight rescheduled for a later visit. Of these 17, eight reported improved smell and taste function. No patient dropped out of the study due to drug side effects.

Although present results indicate improvement in sensory function similar to that in the pilot study and better than in the oral theophylline study a placebo controlled randomized double-blind clinical trial at several sites is necessary to confirm these results [7,13]. However, the reported and measured lack of improvement in a significant number of patients who took intranasal theophylline is consistent with the reliability of the present study in improving smell function in the majority of these hyposmic patients.

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