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Research Article

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The Dynamics of Hyposmia and Results of Treatment with Intranasal Theophylline

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Abstract

Objective: We recently demonstrated efficacy of intranasal theophylline in treatment of hyposmia in a large, diverse group of patients who exhibited this abnormality over an extended time period. Because hyposmia is long lasting we wished to evaluate hyposmia severity among patients related to length of time they exhibited hyposmia prior to initial evaluation and to whether hyposmia length or severity influenced treatment efficacy.

Methods: Ninety-four patients with hyposmia were studied. Thirty-two had hyposmia for < 12 months prior to treatment whereas 62 had hyposmia >12 months before treatment. Treatment was intranasal delivery of 20 µg theophylline twice into each nostril once daily for two-12 months. Subjective responses, olfactometry and gustometry were obtained before and after treatment.

Results: Hyposmia was similar in severity degree in both patient groups whether they exhibited hyposmia < or > 12 months after hyposmia onset. However, treatment with intranasal theophylline resulted in greater improvement in patients with onset < 12 months.

Conclusions: Whereas degree of hyposmia severity does not differ with respect to length of dysfunction prior to treatment, treatment with intranasal theophylline was more effective in patients who exhibited hyposmia for shorter time periods - the earlier the treatment the better the result.

Key words: *Hyposmia; Hypogeusia; Smell loss; Flavor loss; Theophylline*

Introduction

Patients develop loss of smell as a result of many different pathological events [1-4]. In most patients this loss may be transient but in others it may persist. With the persistence of smell loss patients may seek medical assistance to correct this loss. Some patients may wait weeks or months after their loss to seek help whereas others may seek help quickly in order to recover their smell function.

We have evaluated patients with hyposmia at The Taste and Smell Clinic in Washington DC for over 40 years. Because patients with hyposmia exhibited this abnormality for varying periods of time we wondered if there was any difference in severity of smell loss if patients sought treatment sooner or later after this loss occurred. Because treatment with intranasal theophylline has shown to improve smell function in patients with hyposmia (5) we also wondered if

this treatment to correct hyposmia had any differential effect if initiated soon after the loss occurred or later after the loss was present for an extended period of time.

To answer these questions we compared smell and taste function in patients with hyposmia who presented to The Taste and Smell Clinic in Washington D.C. < one year after initiation and persistence of their loss with patients whose loss extended from > one year to > 30 years after initiation and persistence of their dysfunction.

Methods

Patients

Ninety-four patients [(41women, 53 men, aged 18-85y, 60±2y) (mean±SEM)] presented to The Taste and Smell Clinic for evaluation and treatment of hyposmia. 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 hyposmia for periods of 2 - 780 months (77±13 months) prior to their first visit to The Clinic. We divided patients into two groups – one group, 32 patients (34%), sought treatment < 12 months after initiation of hyposmia whereas the second group, 62 patients (66%), sought treatment greater than one year after initiation of hyposmia. Clinical history was consistent with several etiologies of smell dysfunction: post-influenza-like illness [(PIHH) (29 patients) [6]], allergic rhinitis (31 patients) [7], head injury (13 patients) [8], congenital loss of smell (5 patients) [9] and various other causes (16 patients) [4]. Physical examination of the head and neck was within normal limits in each patient including nasal endoscopy of upper airways. 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 [4] and standard specific tests of olfactometry [4] and gustometry [4] before treatment and at intervals of two- twelve months after therapy initiation.

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]. 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.

Olfactometry [4] consisted of measuring smell function by use of standard techniques [4] 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). 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. The validity of these techniques were demonstrated in a double blind clinical trial (10).

Gustometry [4] 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.

Patients were treated with intranasal theophylline and evaluated prior to treatment and at intervals of two – 12 months in periods of two-four months, five-eight months and nine-12 months after treatment [9]. 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. 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.

Intranasal theophylline was prepared by a contract pharmacy (Boothwyn Pharmacy, Upper Chichester, PA). Twenty µg of theophylline, in a solution containing an aqueous solution of theophylline with pharmacologically common excipients delivered in a metered dose of 100 µL was inserted twice into each nostril 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.

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

Results

Clinical characteristic of each patient group are shown in Tables I and II. The length of loss prior to treatment is significantly longer in the >12 month (65±2 mo) than in the <12 month group (5.7±0.5 mo) as expected. Clinical characteristics of the two groups indicated that there were about twice the number of men in the >12 month than in the <12 month group, patients with congenital smell loss were in the <12 month group [Table II]. There were five times as many patients with allergic rhinitis in the > 12 month group than in the <12 month group [Table II]. The age range as expected, was larger in the >12 month group due to the presence of all the congenital patients in this group although the mean age is not significantly different between the two groups ($p > 0.05$).

	Age (y)	Gender		Mean Loss Length
Group		Men	Women	Before Treatment (mo)
< 12 months	65 ± 2* (25-82)	15	17	5.7 ± 0.5
> 12 months	58 ± 2 (13-85)	39	23	114 ± 18a

*Mean ± SEM

( ) age range

[a]p<0.001 comparison with < 12 month group

Table I: *Characteristics of Treatment Groups.*

Pathology	< 12 Months	> 12 Months
PIHH	14[+]	15
Allergic rhinitis	5	26
Head injury	8	5
Congenital	0	5
Idiopathic	2	6
Other	3	5

[+]Patient Number

Table II: *Clinical Pathology of Treatment Groups.*

Condition	Taste		Flavor		Smell	
	Acuity	Patient Number Improved (%)	Acuity	Patient Number Improved (%)	Acuity	Patient Number Improved (%)
2-4 Month Treatment						
<12 months (31)	6±2*	23 (74)	8±2	23 (74)	9±3	23 (74)
> 12 months (58)	11±3	34 (58)	6±3	34 (58)	5±2	34 (58)
5-8 Month Treatment						
<12 months (27)	17±3	20 (74)	15±4	20 (74)	10±3	20 (74)
>12 months (50)	13±3	32 (64)	11±3	32 (64)	11±2	32 (64)
9-12 Month Treatment						
<12 months (15)	20±5	13 (87)	22±5	13 (87)	18±4	13 (87)
> 12 months (41)	19±4	33 (80)	16±4	33 (80)	14±4	33 (80)

*Mean ± SEM

( ) patient number

With respect to > 12 months improvement

$X^2 = 16.0$, $p<0.01$

Table III: *Comparison of Subjective Changes in Sensory Function in Hyposmic Patients < Or > 12 Months after Hyposmic Onset Treated with Intranasal Theophylline.*

Subjective perception of smell, flavor and smell function prior to treatment was similar in both patient groups regardless of the time of hyposmia onset.

Comparison of subjective changes in taste, flavor and smell at each treatment interval, except after 5-8 months of treatment for smell function, showed that responsiveness for taste, flavor and smell improved more among patients who exhibited their dysfunction < 12 months than among those in > 12 month group [(X^2, $p<0.01$), non parametric analysis, Table III] . While patients in both groups reported improvement in taste, flavor, and smell function as treatment time progressed acuity for each parameter increased with the greatest increase reported after the longest treatment period [9-12 months, [Table III]] and with the greatest improvement reported in the < 12 month group.

There was a progressive relative increase in patient number who reported subjective improvement on treatment in the <12 month group compared to those in > 12 month group [Table III]. Indeed, over time relatively more patients in the < 12 month group reported subjective improvement while fewer in >12 month group did so.

For gustometry prior to treatment responsiveness to most tastants was more sensitive (increased acuity) in the < 12 month group but these differences were not significant [($X^2 > 0.05$) non parametric study [Table IV]]. This indicates that the length of hyposmia prior to treatment did not influence subjective taste responsiveness [Table IV]. However, with treatment, while both groups improved subjectively there was greater improvement in the < 12 month treatment group compared to the <12 month group [(9 of 9 parameters improved) non parametric study, $X^2 < 0.01$)]. For olfactometry, prior to treatment, responsiveness for all odors was similar in both patient groups [Table V]. While there was improvement in olfaction in both patient groups treatment for two-four and 4-8 months showed no difference in responsiveness between the two groups [Table V]. However, after 9-12 months of treatment patients in the < 12 month group demonstrated significant improvement in olfactometry compared to responses of the > 12 month group which was demonstrated by significant improvement in olfaction for all odorants [Table V]. Indeed, in the <12 month group at 9-12 months many smell parameters had returned to normal levels whereas those in the > 12 months group were improved but remained at less sensitive levels [Table V].

Condition	NaCL				SUCROSE				HCL				UREA			
Untreated	**DT**	**RT**	**ME**	**H**	**DT**	**RT**	**ME**	**H**	**DT**	**RT**	**ME**	**H**	**DT**	**RT**	**ME**	**H**
<12 months (32)	5.13 ±0.35*	5.31 ±0.38	43 ±4	-19 ±4	4.53 ±0.36	4.59 ±0.36	38 ±4	25 ±5	4.75 ±0.28	5.03 ±0.31	45 ±4	-32 ±5	4.97 ±0.43	5.28 ±0.48	39 ±4	-35 ±4
>12 months (62)	4.50 ±0.20	4.74 ±0.24	48 ±3	-18 ±3	4.08 ±0.20	4.19 ±0.19	41 ±2	15 ±4	4.40 ±0.20	4.53 ±0.20	47 ±2	-22 ±4	4.74 ±0.29	4.85 ±0.29	39 ±3	-29 ±3
p	0.10	0.19	0.26	0.92	0.23	0.29	0.52	0.14	0.32	0.17	0.65	0.14	0.65	0.43	0.96	0.27
Treated	DT	RT	ME	H	DT	RT	ME	H	DT	RT	ME	H	DT	RT	ME	H
2-4 months																
<12 months (31)	4.68 ±0.37	4.87 ±0.36	48 ±4	-22 ±5	4.23 ±0.35	4.29 ±0.34	42 ±4	17 ±6	3.97 ±0.28	4.26 ±0.29	48 ±4	-36 ±5	4.29 ±0.46	4.48 ±0.49	47 ±5	-42 ±5
>12 months (58)	4.33 ±0.21	4.48 ±0.21	47 ±3	-18 ±4	3.79 ±0.19	3.86 ±0.19	42 ±3	16 ±4	3.84 ±0.21	4.03 ±0.21	46 ±3	-27 ±4	4.36 ±0.27	4.34 ±0.26	42 ±3	-33 ±3
p	0.38	0.32	0.81	0.56	0.23	0.23	0.97	0.92	0.73	0.54	0.69	0.14	0.89	0.78	0.44	0.13
5-8 months	DT	RT	ME	H	DT	RT	ME	H	DT	RT	ME	H	DT	RT	ME	H
<12 months (27)	4.67 ±0.40	4.85 ±0.42	51 ±5	-26 ±6	3.93 ±0.30	4.07 ±0.28	46 ±5	15 ±8	4.00 ±0.27	4.07 ±0.27	50 ±5	-34 ±6	4.04 ±0.42	4.04 ±0.42	48 ±6	-39 ±6
>12 months (50)	4.36 ±0.23	4.56 ±0.25	49 ±3	-23 ±4	3.80 ±0.20	3.90 ±0.18	42 ±3	14 ±4	4.00 ±0.23	4.18 ±0.23	48 ±3	-29 ±4	4.22 ±0.31	4.30 ±0.31	43 ±3	-44 ±11
p	0.47	0.52	0.78	0.71	0.72	0.58	0.54	0.91	1.0	0.78	0.73	0.50	0.73	0.61	0.40	0.77
9-12 months	DT	RT	ME	H	DT	RT	ME	H	DT	RT	ME	H	DT	RT	ME	H

<12 months (15)	4.20 ±0.71	4.27 ±0.72	53 ±7	-35 ±7	3.80 ±0.61	3.87 ±0.61	40 ±6	26 ±7	4.13 ±0.43	4.27 ±0.45	47 ±6	-34 ±6	4.13 ±0.70	4.13 ±0.70	46 ±7	-40 ±7
>12 months (41)	4.27 ±0.28	4.34 ±0.27	49 ±4	-23 ±4	3.88 ±0.23	3.98 ±0.23	38 ±3	13 ±4	4.02 ±0.26	4.12 ±0.26	41 ±3	-25 ±3	4.22 ±0.32	4.22 ±0.32	40 ±3	-29 ±4
p	0.91	0.90	0.61	0.19	0.88	0.84	0.75	0.13	0.83	0.78	0.38	0.17	0.90	0.90	0.39	0.20

*Mean±SEM

( ) patient number

Table IV: *Comparison of Taste Responses in All Hyposmic Patients with Hyposmia < 12 Months or > 12 Months after Loss Onset Related to Before and After Intranasal Theophylline Treatment*

Condition	**Pyridine**				**Nitrobenzene**				**Thiophene**				**Amyl acetate**			
Untreated	**DT**	**RT**	**ME**	**H**	**DT**	**RT**	**ME**	**H**	**DT**	**RT**	**ME**	**H**	**DT**	**RT**	**ME**	**H**
<12 months (32)	7.41 ± 0.40*	8.31 ±0.48	30 ±5	-28 ±5	7.81 ±0.62	8.88 ±0.60	10 ±3	0 ±2	7.41 ± 0.70	8.03 ±0.66	19 ±4	-13 ±3	7.59 ±0.66	8.81 ±0.55	11 ±3	-2 ±2
>12 months (62)	7.34 ±0.43	8.29 ±0.41	28 ±3	-20 ±4	7.77 ±0.49	8.31 ±0.49	13 ±2	2 ±2	7.48 ± 0.49	7.87 ±0.52	16 ±3	-10 ±3	7.55 ±0.51	8.50 ±0.51	11 ±2	2 ±2
p	0.92	0.97	0.75	0.23	0.96	0.49	0.51	0.47	0.93	0.85	0.44	0.58	0.96	0.70	1.0	0.17
Treated	DT	RT	ME	H	DT	RT	ME	H	DT	RT	ME	H	DT	RT	ME	H
2-4 months																
<12 months (31)	5.48 ±0.61	6.45 ±0.67	37 ±5	-34 ±5	5.84 ±0.76	6.58 ±0.75	25 ±5	-7[c] ±5	5.29 ±0.75	5.77 ±0.81	28 ±5	-23 ±5	5.71 ±0.74	6.55 ±0.71	27[d] ±5	-4[d] ±5
>12 months (58)	6.64 ±0.46	7.40 ±0.43	34 ±4	-28 ±3	6.81 ±0.50	7.29 ±0.53	18 ±3	5 ±2	6.43 ±0.51	6.95 ±0.52	23 ±3	-13 ±3	6.79 ±0.52	7.34 ±0.53	16 ±2	6 ±2
p	0.14	0.22	0.63	0.29	0.27	0.44	0.20	0.01	0.20	0.21	0.35	0.09	0.23	0.38	0.04	0.02
5-8 months	DT	RT	ME	H	DT	RT	ME	H	DT	RT	ME	H	DT	RT	ME	H
<12 months (27)	4.93 ±0.75	5.56 ±0.86	34 ±6	-28 ±6	5.44 ±0.90	6.19 ±0.89	25 ±6	1 ±5	4.96 ±0.83	5.85 ±0.91	26 ±5	-21 ±6	5.11 ±0.87	6.11 ±0.88	25 ±5	0 ±5
>12 months (50)	6.26 ±0.52	6.74 ±0.51	33 ±4	-26 ±4	6.50 ±0.58	6.78 ±0.61	19 ±3	4 ±2	6.06 ±0.56	6.50 ±0.57	24 ±3	-14 ±4	6.12 ±0.60	6.54 ±0.60	19 ±3	4 ±3
p	0.14	0.21	0.86	0.82	0.31	0.57	0.32	0.60	0.27	0.53	0.71	0.23	0.33	0.68	0.34	0.43
9-12 months	DT	RT	ME	H	DT	RT	ME	H	DT	RT	ME	H	DT	RT	ME	H
<12 months (15)	3.60[c] ±0.94	3.87[d] ±1.00	43 ±8	-37 ±9	3.73d ±0.94	5.47 ±1.02	34 ±8	-14[c] ±8	3.33[c] ±0.92	3.80[d] ±1.08	42[d] ±9	-37[a] ±10	3.33[c] ±0.89	5.27 ±1.07	37[d] ±8	-10 ±7
>12 months (41)	6.63 ±0.58	6.83 ±0.61	32 ±4	-26 ±4	6.49 ±0.66	6.73 ±0.69	19 ±4	3 ±3	6.49 ± 0.65	6.73 ±0.68	22 ±4	-12 ±4	6.56 ±0.68	6.80 ±0.68	20 ±4	0 ±3
p	0.01	0.02	0.23	0.21	0.03	0.33	0.06	0.01	0.01	0.03	0.02	0.004	0.01	0.24	0.04	0.16

* Mean±SEM

( ) patient number

With respect to >12 months

a p<0.001

b p<0.005

c p<0.01

d p<0.05

Table V: *Comparison of Smell Responses in All Hyposmic Patients Evaluated <12 Months or >12 Months after Loss Onset and Subsequent Theophylline Treatment.*

Discussion

Results of this study demonstrate two important concepts. The first demonstrates that regardless of the length of hyposmia onset prior to treatment there is no difference in sensitivity of loss even for periods as short as two months or as long as 780 months. This indicates that once hyposmia occurs, and is confirmed, it tends to persist at the same insensitive level.

By history, many patients who develop hyposmia recover spontaneously. This is particularly common in patients who experience smell loss in association with a coryza or upper respiratory illness. With onset of this illness smell loss is commonly initiated with nasal congestion and blockage of passage of odorants to the olfactory epithelium; with remission of the nasal blockage and recovery from the coryza, olfactory function usually returns to its prior normal state. Only a small percentage of patients proceed to persistent hyposmia and many do not seek treatment for their transient smell loss. Patients evaluated at The Taste and Smell Clinic in Washington D.C. are those who have had a persistent loss of smell for two months or more (mean length 5.7±0.5 mo) and who have reported no spontaneous return of smell function during this period. Indeed, there are only a few reports of spontaneous return of smell function in patients who have developed hyposmia for extended time periods after the loss occurs [11-13] and it is unlikely that among the < 12 month patients in this study there was any spontaneous return of function. This is demonstrated by the lack of significant improvement in olfaction at the 2-4 and 5-8 month treatment periods; only after 9-12 months did significant improvement in olfactometry improvement occur.

The second important concept indicates that treatment with intranasal theophylline in patients who have hyposmia for <12 months prior to treatment responded better with greater sensitivity than did patients who had hyposmia for >12 months. Indeed, mean olfactory sensitivity for all odors returned to the normal range in the >12 month patients compared to the >12 month patients. This is confirmed by subjective responses for taste, flavor and smell and for olfactometry responses which were significantly more sensitive in the <12 months group compared to the >12 months group.

Level of Evidence: Open label controlled clinical trial

Conflict of Interest: Robert I. Henkin is a member of the board of directors of Cyrano Therapeutics. The other author has no conflict of interest, financial or otherwise with respect to the publication of this manuscript.

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