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Age is Unrelated to Hyposmia Onset or Its Treatment with Intranasal Theophylline

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Abstract

Purpose: We recently demonstrated efficacy of intranasal Theophylline in the treatment of smell dysfunction in a large, diverse group of patients who exhibited this abnormality. Because age has been reported to be a factor in Hyposmia onset in the general population it was of interest to evaluate Hyposmia and age in a patient group who exhibited Hyposmia before and after treatment with intranasal Theophylline.

Methods: Ninety-four patients with smell dysfunction were studied. Of these patients 43 were <65 years of age whereas 51 were >65 years of age. All patients were initially studied without treatment. They were then treated with 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: Smell loss was similar in both patient groups prior to treatment: Smell function was significantly impaired compared to normal subjects. After treatment Hyposmia improved in both groups to the same degree with acuity returning toward or to the normal range in both patient groups.

Conclusion: These results indicate that Hyposmia is of similar magnitude in patients <or> age 65 prior to any treatment and that after treatment with intranasal Theophylline acuity is of similar efficacy in patients <or> 65 years of age indicating that age is not a factor either in onset or in ability to correct Hyposmia.

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

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Introduction

It has been previously reported that age is a major factor associated with smell loss (Hyposmia) in the general population with older patients (generally ≥ 65 years of age) frequently exhibiting smell loss compared to younger patients [1-4].

We have studied smell loss in a large group of Hyposmia patients over the past 40 years and in a smaller group of hyposmic patients who have recently been treated with intranasal Theophylline in an attempt to improve their smell loss [5,6]. Whereas this therapy has been successful in improving Hyposmia in this smaller group of patients we wondered if age were a factor in onset of their Hyposmia and if treatment in this smaller group of patients differed with respect to age.

To answer this question we divided these patients into two groups, one aged 65 years and over and the other under 65 years to evaluate their initial olfactory status and their response to intranasal Theophylline therapy. Results indicated that age is not a factor in either onset of Hyposmia or its treatment with intranasal Theophylline.

Methods

Patients

Ninety-four patients [(41-women, 53-men, aged 18 years to 85 years, 60 y ± 2 y) (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 months ± 13 months) prior to their first visit to The Clinic. Of these patients, the youngest group consisted of 24 men, 19 women (47 ± 2 mean ± SEM y), whereas the older

Table 1: Comparison of hyposmic patients characterized by age prior to treatment with intranasal Theophylline compared to normal subjects.

Age (y)	Range	PYRIDINE				NITROBENZENE				THIOPHENE				AMYL ACETATE			
		DT	RT	ME	H	DT	RT	ME	H	DT	RT	ME	H	DT	RT	ME	H
<65(43)	13-63	7.35+a ± 0.51	8.56a ± 0.50	33‡a ± 5	-26a ± 5	8.14a ± 0.61	8.65a ± 0.63	13a ± 3	-1 ± 2	7.72a ± 0.64	8.37a ± 0.66	17 ± 4	-13 ± 4	8.21a ± 0.63	8.88a ± 0.62	11a ± 3	1 ± 2
>65(51)	65-85	7.37a ± 0.39	8.08a ± 0.40	24a ± 3	-20a ± 3	7.49a ± 0.49	8.37a ± 0.47	11a ± 2	2 ± 2	7.24a ± 0.51	7.55a ± 0.51	17 ± 3	-9 ± 2	7.02a ± 0.51	8.37a ± 0.48	11a ± 2	2 ± 2
Normal subjects (55)	18-82	4.4 ± 0.50	5.8 ± 0.10	66 ± 5	-51 ± 5	4.1 ± 0.20	5.9 ± 0.20	52 ± 6	3 ± 3	3.8 ± 0.10	5.4 ± 0.20	7 ± 8	-59 ± 4	3.9 ± 0.10	5.1 ± 0.20	53 ± 5	5 ± 1

(Patient number) + Mean ± SEM (in bottle units)
‡Mean ± SEM (in %)
With respect to normal's a p<0.001

Table 2: Subjective improvement to intranasal Theophylline treatment in hyposmic patients characterized by age.

PERIOD [mo]	TASTE (%)	FLAVOR (%)	SMELL (%)	AGE (y) range	
<65(39) [2-4]	10+ ± 3	8 ± 3	6 ± 2	48 ± 2	17-63
>65(50) [2-4]	9 ± 3	6 ± 3	6 ± 3	72 ± 1	65-85
<65(38) [5-8]	11 ± 3	10 ± 3	8 ± 2	47 ± 2	13-63
>65(39) [5-8]	18 ± 4	14 ± 4	13 ± 3	72 ± 1	65-85
<65(30) [9-12])	19 ± 4	17 ± 4	17 ± 4	44 ± 2	13-63
>65(26) [9-12]	20 ± 5	18 ± 4	13 ± 4	72 ± 1	65-85

(patient number) +Mean ± SEM

group consisted of 29 men, 22 women (72 y ± 1 y). Clinical history was consistent with several etiologies of smell dysfunction: Post-influenza-like illness [(PIHH) (29 patients) [7]], allergic rhinitis (31 patients) [8], head injury (13 patients) [9], congenital loss of smell (5 patients) [10] and various other causes (16 patients) [5]. 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 [9]. 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 consisted of measuring smell function by use of standard techniques by determination of Detection Thresholds (DT), Recognition Thresholds (RT), Magnitude Estimation (ME) and Hedonics (H) for four odorants [4,9]: 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.

Patients were treated with intranasal Theophylline and evaluated prior to treatment and at intervals of two to twelve months in periods of two-four months, five-eight months and nine- twelve 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). The 20 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

Olfactometry results in hyposmic patients at initial evaluation of their Hyposmia characterized by age (<and> age 65 y) compared to normal subjects are shown in Table 1. Results indicate that there are no differences in olfactometry between the two groups with both groups demonstrating significantly less sensitivity in each olfaction category compared to normal subjects.

Subjective responses to treatment of hyposmic patients categorized by age are shown in Table 2. As treatment proceeded in time both patient groups demonstrated improvement in taste, flavor and smell function although there are no differences in responsiveness between each patient group.

Table 3: Olfactometer differences after intranasal Theophylline treatment of hyposmic patients characterized by age.

Period (mo)	PYRIDINE				NITROBENZENE				THIOPHENE				AMYL ACETATE			
2-4	DT	RT	ME	H	DT	RT	ME	H	DT	RT	ME	H	DT	RT	ME	H
<65(39)	6.26* ± 0.61	7.15 ± 0.59	39‡ ± 5	-34 ± 5	6.85 ± 0.65	7.67 ± 0.67	21 ± 4	2 ± 3	6.26 ± 0.65	6.87 ± 0.69	26 ± 4	-17 ± 5	6.97 ± 0.67	7.82 ± 0.65	20 ± 4	1 ± 4
>65(50)	6.22 ± 0.46	7 ± 0.46	32 ± 4	-27 ± 3	6.18 ± 0.55	6.56 ± 0.56	19 ± 3	1 ± 3	5.86 ± 0.57	6.28 ± 0.58	24 ± 3	-16 ± 3	5.98 ± 0.55	6.48 ± 0.56	20 ± 3	4 ± 3
5-8	DT	RT	ME	H	DT	RT	ME	H	DT	RT	ME	H	DT	RT	ME	H
<65(38)	5.97 ± 0.61	6.66 ± 0.66	34 ± 5	-28 ± 5	6.71 ± 0.72	7.18 ± 0.75	21 ± 4	4 ± 3	6.18 ± 0.70	6.53 ± 0.75	25 ± 5	-17 ± 5	6.42 ± 0.78	7.24 ± 0.74	23 ± 4	4 ± 1
>65(39)	5.62 ± 0.61	6 ± 0.62	32 ± 4	-25 ± 5	5.56 ± 0.66	5.97 ± 0.66	20 ± 4	2 ± 3	5.18 ± 0.62	6.03 ± 0.62	24 ± 4	-16 ± 4	5.13 ± 0.61	5.56 ± 0.64	20 ± 3	1 ± 3
9-12	DT	RT	ME	H	DT	RT	ME	H	DT	RT	ME	H	DT	RT	ME	H
<65(30)	5.7 ± 0.72	6.03 ± 0.77	45 ± 5	-39 ± 5	5.93 ± 0.80	6.43 ± 0.81	26 ± 5	1 ± 4	5.73 ± 0.79	6.13 ± 0.86	31 ± 6	-19 ± 6	6.17 ± 0.85	6.6 ± 0.84	29 ± 6	-2 ± 4
>65(26)	5.96 ± 0.78	6.04 ± 0.79	23 ± 5	-17 ± 5	5.54 ± 0.81	6.35 ± 0.81	19 ± 5	-5 ± 4	5.54 ± 0.82	5.73 ± 0.84	23 ± 6	-18 ± 6	5.15 ± 0.79	6.15 ± 0.81	19 ± 5	-4 ± 4

(Patient number) + Mean ± SEM (in bottle units)
‡ Mean ± SEM (in %)

Olfactometry differences in hyposmic patients categorized by age in relationship to treatment with intranasal Theophylline are shown in Table 3. While DT and RT for all parameters are elevated above normal, ME for all parameters are less than normal and H for unpleasant odors are less than normal, as are H for odors for pleasant odors, there are no differences between the two patient groups. Indeed, responses for DT and RT for each parameter improved into the normal range after 5 to 8 months of treatment. While each parameter of smell function improved in each patient group over a period of 12 months there were no differences in treatment responses categorized by age.

Discussion

Results of this study demonstrate two important concepts. The first demonstrates that regardless of the age of patients at hyposmia onset prior to treatment there were no differences in sensitivity of loss at their presentation to The Taste and Smell Clinic in Washington, DC. This indicates that Hyposmia onset is unrelated to onset age in this hyposmic patient group irrespective of the etiology of their Hyposmia.

The second important concept indicates that treatment with intranasal Theophylline in hyposmic patients improves hyposmia and is unrelated to patient age. Indeed, olfactory sensitivity for all odors as shown by olfactometry returned toward or to the normal range in both patient groups as treatment continued and olfactometry responses were significantly more sensitive in both patient groups with intranasal Theophylline treatment.

While among a general population of people older patients may exhibit loss of smell more frequently than younger groups in a population of hyposmic patients these data indicate that no matter how old you are when you develop hyposmia there is no difference in Hyposmia related to age and that intranasal Theophylline can be effective treatment to improve smell function in both groups irrespective of age.

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