

# Intranasal Theophylline Treatment of Hyposmia and Hypogeusia

## A Pilot Study

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**Objective:** To determine whether intranasal theophylline methylpropyl paraben can correct hyposmia and hypogeusia.

**Design:** We performed an open-label pilot study in patients with hyposmia and hypogeusia under the following 3 conditions: (1) before treatment, (2) after oral theophylline anhydrous treatment, and (3) after intranasal theophylline treatment. Under each condition, we performed subjective evaluations of taste and smell functions, quantitative measurements of taste (gustometry) and smell (olfactometry), and measurements of serum theophylline level and body weight.

**Setting:** The Taste and Smell Clinic in Washington, DC.

**Patients:** Ten patients with hyposmia and hypogeusia clinically related to the effects of viral illness, allergic rhinitis, traumatic brain injury, congenital hyposmia, and other chronic disease processes were selected.

**Interventions:** Oral theophylline anhydrous, 200 to 800 mg/d for 2 to 12 months, was administered to each patient. This treatment was discontinued for 3 weeks to 4

months when intranasal theophylline methylpropyl paraben, 20 µg/d in each naris, was administered for 4 weeks.

**Main Outcome Measures:** At termination of each condition, taste and smell function was determined subjectively, by means of gustometry and olfactometry, with measurement of serum theophylline levels and body weight.

**Results:** Oral theophylline treatment improved taste and smell acuity in 6 patients after 2 to 12 months of treatment. Intranasal theophylline treatment improved taste and smell acuity in 8 patients after 4 weeks, with improvement greater than after oral administration. No adverse effects accompanied intranasal drug use. Body weight increased with each treatment but was greater after intranasal than after oral administration.

**Conclusions:** Intranasal theophylline treatment is safer and more effective in improving hyposmia and hypogeusia than oral theophylline anhydrous treatment.

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**L**OSS OF SMELL (HYPOSMIA) and taste (hypogeusia) are common symptoms that affect many thousands of patients in the United States, as reported by several investigators.<sup>1-4</sup> Effective treatment for these symptoms has been demonstrated only recently and has not been formally established.

Before effective treatment to correct loss of smell and taste can be established, a biochemical basis for the cause of these symptoms is necessary. To accomplish this, we determined that these symptoms are commonly caused by decreased secretion of several growth factors in the saliva and nasal mucus. The growth factors act on stem cells in taste buds and olfactory epithelial

cells to generate the elegant repertoire of cellular components in these sensory organs.<sup>5-11</sup> Growth factor stimulation of these sensory organs is thought to maintain normal taste and smell function.<sup>5-11</sup> If these growth factors were diminished by any of several diseases and pathological conditions, then hyposmia and hypogeusia occur.<sup>5,12,13</sup> These conditions and diseases include trace metal deficiencies<sup>14</sup>; vitamin deficiencies<sup>15,16</sup>; liver disease<sup>17</sup>; diabetes mellitus<sup>18</sup>; other metabolic,<sup>12,13</sup> otolaryngological,<sup>19,20</sup> and neurodegenerative disorders, including multiple sclerosis,<sup>21-23</sup> Parkinson disease,<sup>24-28</sup> and Alzheimer disease<sup>29-32</sup>; and other neurological disorders.<sup>33</sup> Effective treatment to increase secretion of these growth factors is therefore

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necessary to improve hypogeusia and hyposmia<sup>5,12,13</sup> and return taste and smell function to normal as demonstrated by several previous studies.<sup>5,12,13</sup>

To understand more about these processes, a comprehensive study of many patients with loss of smell and taste determined that levels of the salivary<sup>34,35</sup> and nasal mucus<sup>36,37</sup> growth factors cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) were lower than in healthy subjects and were responsible for the onset of hyposmia and hypogeusia in many of these patients.<sup>38,39</sup> Indeed, as hyposmia increased in severity, levels of these salivary<sup>35</sup> and nasal mucus<sup>37</sup> growth factors decreased in a consistent manner.

To increase salivary and nasal mucus cAMP and cGMP levels and thereby correct hypogeusia and hyposmia, we hypothesized that treatment with a phosphodiesterase inhibitor would be useful. To test this hypothesis, a previous study from our institution administered oral theophylline anhydrous to 312 patients with hyposmia and hypogeusia in an open-label controlled clinical trial.<sup>40</sup> Results of this study demonstrated that oral theophylline treatment successfully corrected hyposmia in more than 50% of these patients.<sup>40</sup> Subsequent investigators have used other oral phosphodiesterase inhibitors to correct hyposmia.<sup>41</sup> An open-label study also demonstrated that, as nasal mucus cAMP and cGMP levels increased, hyposmia was corrected,<sup>42</sup> whereas in patients in whom these moieties did not increase, hyposmia was not corrected. These results suggested that some patients may be resistant to treatment with oral theophylline.<sup>42</sup>

However, successful treatment with oral theophylline that increased nasal mucus levels of cAMP and cGMP required increased theophylline doses,<sup>40</sup> sometimes prolonged treatment duration,<sup>40</sup> and endurance of adverse effects, including restlessness, gastrointestinal tract discomfort, sleep difficulties, tachycardia, and other unwanted symptoms.<sup>40,43,44</sup> Theophylline treatment also required regular determinations of blood theophylline levels to ensure adequate drug absorption and lack of toxic effects.<sup>40</sup> These efforts limited use of this orally administered drug.

Because of these adverse effects, we wished to learn more about the pharmacology of theophylline administration. After treatment with oral theophylline, the drug was found in blood, nasal mucus, and saliva in a dose-dependent manner.<sup>45</sup> These results were consistent with improvement in smell function as demonstrated in patients with hyposmia in the prior clinical trial.<sup>40</sup> Results of these studies<sup>40,42</sup> and efforts to improve therapeutic efficacy and reduce adverse effects of oral theophylline administration made it logical to administer the drug intranasally. In this manner, the drug could affect olfactory receptors more directly without causing the systemic adverse effects associated with oral therapy.

To accomplish this, with assistance of an established medical device company, an intranasal delivery device was developed. With assistance of an established pharmaceutical company, the drug was packaged for sterile, intranasal delivery. Using this device, an open-label, single-source, controlled pilot study in 10 patients with hyposmia and hypogeusia and with levels of parotid saliva<sup>35,36</sup> and nasal mucus<sup>37,38</sup> cAMP and cGMP below the refer-

ence range was performed to determine safety and to compare smell and taste responses after intranasal theophylline treatment, with patient responses before any treatment and after oral theophylline treatment.

## METHODS

### PATIENTS

We selected 10 patients with hyposmia and hypogeusia from the 312 patients who participated in the prior open-label controlled clinical trial at The Taste and Smell Clinic<sup>40</sup> for this pilot study. Each patient had undergone previous evaluation before any drug treatment,<sup>12,13</sup> followed by treatment with oral theophylline. These patients had hyposmia and hypogeusia and exhibited levels of cAMP and cGMP lower than their respective reference ranges in the saliva<sup>35,36</sup> and nasal mucus<sup>37,38</sup> before theophylline treatment. These 10 patients were selected from the group undergoing previous evaluation and treatment for the intranasal trial because (1) their response to oral theophylline was subjectively submaximal; (2) they developed adverse effects after attempts to increase the drug dose to obtain a more maximal clinical response, thus limiting the administered drug dose; and (3) they resided in an area in close proximity to The Clinic, which made their frequent return visits to The Clinic more practical for any additional clinical trial.

These 10 patients included 7 men, aged 37 to 77 (mean [SEM] age, 64 [6]) years, and 3 women, aged 47 to 77 (62 [11]) years. Patients had 1 of the following 5 different clinical causes of sensory dysfunction: allergic rhinitis<sup>46</sup> (n=3), post-influenzalike hyposmia and hypogeusia<sup>47</sup> (n=3), head injury<sup>48</sup> (n=2), congenital hyposmia<sup>49</sup> (n=1), and other disorders<sup>12,13</sup> (n=1).

Patients served as their own control throughout each condition of this study. The conditions included no treatment (before entry into the oral theophylline study), oral theophylline treatment, and intranasal theophylline treatment.

### PROCEDURES

Subjective changes in smell and taste function under each study condition were measured by questionnaire before measurements of smell or taste function.<sup>40,50</sup> Responses were graded on a scale from 0 to 100, with 0 reflecting no subjective response in overall sensory function; 100, return to normal sensory function; and values between 0 and 100 intermediate responses.<sup>40,50</sup> Overall sensory function was defined as the ability to smell all odors and identify all tastants, although response intensity varied.<sup>40,50</sup>

Smell and taste functions under each study condition were measured by standardized psychophysical sensory testing techniques.<sup>40,50</sup> Measurements included determination of detection thresholds (DTs), recognition thresholds (RTs), magnitude estimation (ME), and hedonic response (HR) for 4 odors (ie, pyridine [dead fish], nitrobenzene [bitter almond], thiophene [petroleum], and amyl acetate [banana oil]) (olfactometry) and for 4 tastants (ie, sodium chloride [salt], sucrose [sweet], hydrochloride [sour], and urea [bitter]) (gustometry). These techniques have been previously described<sup>40</sup> with olfactometry confirmed in a prior controlled double-blind clinical trial.<sup>51</sup> Each measurement was performed independent of any prior knowledge of response.

Serum theophylline levels were measured by fluorescence polarization<sup>40</sup> at each treatment condition. Body weight was measured with a calibrated clinical scale during each study condition and reported at the final measurement in each study condition.

## STUDY PROTOCOL

The patients each underwent initial clinical evaluation at The Clinic to establish the cause, degree, and character of hyposmia and hypogeusia<sup>40</sup> exhibited. Measurements in blood, urine, erythrocytes, saliva, and nasal mucus determined before their entry into the open trial of oral theophylline established the biochemical cause of their hyposmia and hypogeusia to be related to their levels of saliva and nasal mucus cAMP and cGMP being lower than the reference range.<sup>35-38</sup> These 10 patients were then selected for this study on the basis of the laboratory and clinical criteria noted previously.

The 10 patients in this intranasal pilot study entered into the previous oral theophylline study according to a protocol approved by the institutional review board of the Georgetown University Medical Center. In this prior trial, oral theophylline methylpropyl paraben was administered daily in 2 divided doses (at breakfast and lunch) of 200, 400, 600, or 800 mg for 2 to 12 months of treatment.<sup>40</sup> Treatment was divided into 2- to 4-month periods, at which time patients returned to The Clinic for measurements of subjective sensory responses, olfactometry, gustometry, serum theophylline level, and body weight. If oral theophylline treatment failed to correct hyposmia at a given dose, the theophylline methylpropyl paraben dose was increased by 200 mg, and the patient underwent reevaluation at 2- to 4-month intervals to a dose of 800 mg.<sup>40</sup> As noted previously, study patients did not obtain a maximal clinical response to oral theophylline<sup>40</sup> or, while taking oral theophylline at a given dose, demonstrated some clinical improvement but experienced significant adverse effects that limited increasing the oral dose as necessary to achieve maximum clinical benefit. In the 10 patients selected for the intranasal pilot study, oral theophylline treatment was discontinued 3 weeks to 4 months before initiation of the intranasal drug trial. At that time, the mean (SEM) serum theophylline level was unmeasurable in any patient (0 [0] mg/L).

A pilot study of intranasal theophylline treatment was then initiated among these 10 patients. This trial was an investigator-initiated phase 1, open-label, single-source, controlled pilot study. Intranasal drug therapy reflected a compassionate trial of a potentially more useful therapeutic method to improve hyposmia (and hypogeusia) than oral theophylline. Before the intranasal trial, risks and benefits were explained and the patients signed an informed consent.

The intranasal administration device was a calibrated 1-mL syringe fitted with a nozzle that fit comfortably into the anterior naris (Wolfe Tory Medical, Inc) and loaded under sterile conditions with 20 µg of theophylline methylpropyl paraben in a 0.4-mL saline solution (Foundation Care). Patients were instructed to direct the spray superiorly into the nasal cavity but not posteriorly into the nasopharynx. This technique was practiced before study initiation with sterile saline. Each patient used the technique easily and as demonstrated before drug administration.

Each patient delivered the theophylline dose in each naris once daily throughout the study. Patients underwent evaluation 1, 2, and 4 weeks during drug use with the same measurements used for the oral study.<sup>40</sup>

Values for the oral trial were taken from the last measurements made before discontinuation of oral drug treatment and before initiation of the intranasal trial. This period varied from 2 to 12 months after oral treatment initiation and reflected the maximal improvement in sensory function each patient experienced. Values for the intranasal pilot study were taken from measurements obtained after completion of 4 weeks of intranasal treatment.

The mean and standard error of the mean for all values obtained at each study condition were compared. Differences were

considered significant if  $P < .05$  by the unpaired  $t$  test. Paired comparison tests were also used with differences considered significant if  $P < .05$  by the  $t$  test.

## RESULTS

With oral theophylline administration, hypogeusia improved after 2 to 12 months of treatment, but hypogeusia improved further within 1 to 4 weeks of intranasal treatment (**Table 1**). Results of gustometry after oral and intranasal theophylline are shown in Table 1. Before treatment, DTs for sucrose, hydrochloride, and urea (less sensitive) and RTs for all tastants were elevated (less sensitive) above the reference levels. Magnitude estimations for all tastants were lower (less sensitive) than the reference level. Hedonic responses for sodium chloride, hydrochloride, and urea were lower (less unpleasant) than the reference levels. After oral theophylline treatment, DTs for sucrose and hydrochloride and RTs for sodium chloride, hydrochloride, and urea decreased (more sensitive). Magnitude estimations for all tastants increased (more sensitive) and HR for hydrochloride and urea increased (more unpleasant) as previously reported.<sup>40</sup> After intranasal theophylline treatment, DTs and RTs for all tastants were lower (more sensitive) than before treatment or after oral theophylline treatment. Magnitude estimations for all tastants after intranasal theophylline treatment were higher (more intense) than before any treatment or after oral theophylline treatment. Hedonic responses for sodium chloride, hydrochloride, and urea were more negative (more unpleasant), whereas HRs for sucrose were more positive (more pleasant) than before any treatment or after oral theophylline treatment.

After oral theophylline treatment, hyposmia improved with 2 to 12 months of treatment but improved more with intranasal theophylline after 1 to 4 weeks of treatment (**Table 2**). Olfactometry comparisons of oral and intranasal theophylline treatment are shown in Table 2. Before treatment, compared with reference levels, DTs and RTs for all odorants were elevated (less sensitive); MEs for all odorants were decreased (less sensitive); HRs for pyridine and thiophene were decreased (less unpleasant); and HRs for nitrobenzene and amyl acetate were decreased (less pleasant). After oral theophylline treatment, DTs and RTs for all odorants were decreased (more sensitive), MEs for all odorants were increased (more sensitive), and HRs for all odorants increased (for pyridine and thiophene, more unpleasant; for nitrobenzene and amyl acetate, more pleasant) as previously reported.<sup>40</sup> After intranasal theophylline treatment, DTs and RTs for each odor were lower (more sensitive) than before treatment or after oral theophylline treatment. Magnitude estimations for each odor were higher (more intense) than before treatment or after oral theophylline treatment. Hedonic responses to thiophene were more negative (more unpleasant) and to nitrobenzene were more positive (more pleasant) than before treatment or after oral theophylline treatment.

Smell and taste acuity were reported to be subjectively improved with oral theophylline treatment, but greater improvement was reported after 4 weeks of in-

**Table 1. Gustometry in Patients With Hyposmia and Hypogeusia Before and After Treatment With Oral and Intranasal Theophylline**

| Condition                                                                 | Gustometry, Mean (SEM) |              |            |             |                             |                           |            |            |                               |                             |                        |             |                             |                           |                         |                          |
|---------------------------------------------------------------------------|------------------------|--------------|------------|-------------|-----------------------------|---------------------------|------------|------------|-------------------------------|-----------------------------|------------------------|-------------|-----------------------------|---------------------------|-------------------------|--------------------------|
|                                                                           | Sodium Chloride        |              |            |             | Sucrose                     |                           |            |            | Hydrochloride                 |                             |                        |             | Urea                        |                           |                         |                          |
|                                                                           | BU, mmol/L             |              | %          |             | BU, mmol/L                  |                           | %          |            | BU, mmol/L                    |                             | %                      |             | BU, mmol/L                  |                           | %                       |                          |
|                                                                           | DT                     | RT           | ME         | HR          | DT                          | RT                        | ME         | HR         | DT                            | RT                          | ME                     | HR          | DT                          | RT                        | ME                      | HR                       |
| Before treatment                                                          | 3.3<br>(0.2)           | 3.6<br>(0.3) | 46<br>(12) | -38<br>(10) | 3.6<br>(0.3)                | 3.8<br>(0.3)              | 38<br>(10) | 28<br>(10) | 4.2<br>(0.4)                  | 5.2<br>(0.7)                | 38<br>(9) <sup>a</sup> | -28<br>(7)  | 5.1<br>(0.3) <sup>b</sup>   | 5.4<br>(0.5)              | 32<br>(8) <sup>c</sup>  | -27<br>(8) <sup>c</sup>  |
| After oral theophylline andhydrous treatment <sup>d</sup>                 | 3.3<br>(0.2)           | 3.3<br>(0.2) | 48<br>(9)  | -35<br>(10) | 3.5<br>(0.2)                | 4.0<br>(1.0)              | 40<br>(10) | 28<br>(9)  | 3.5<br>(0.2)                  | 3.5<br>(0.2) <sup>e</sup>   | 44<br>(10)             | -32<br>(9)  | 4.3<br>(0.2) <sup>e</sup>   | 4.6<br>(0.4)              | 34<br>(11) <sup>c</sup> | -33<br>(11) <sup>a</sup> |
| After intranasal theophylline methylpropyl paraben treatment <sup>f</sup> | 2.6<br>(0.4)           | 3.2<br>(0.3) | 57<br>(11) | -48<br>(11) | 2.2<br>(0.3) <sup>g,h</sup> | 2.4<br>(0.3) <sup>g</sup> | 50<br>(12) | 34<br>(12) | 2.1<br>(0.4) <sup>h,i,j</sup> | 2.6<br>(0.4) <sup>g,h</sup> | 52<br>(10)             | -37<br>(10) | 3.2<br>(0.5) <sup>l,k</sup> | 3.7<br>(0.6) <sup>g</sup> | 42<br>(9) <sup>j</sup>  | -37<br>(10) <sup>a</sup> |
| Reference level                                                           | 3.3<br>(0.3)           | 3.4<br>(0.2) | 68<br>(4)  | -51<br>(4)  | 3.3<br>(0.2)                | 3.4<br>(0.2)              | 60<br>(4)  | 26<br>(3)  | 3.4<br>(0.4)                  | 3.5<br>(0.4)                | 66<br>(4)              | -59<br>(3)  | 3.6<br>(0.4)                | 3.7<br>(0.4)              | 68<br>(4)               | -66<br>(3)               |

Abbreviations: BU, bottle units<sup>13,40</sup>; DT, detection threshold; HR, arithmetic mean hedonic response; ME, mean magnitude estimation response; RT, recognition threshold.

<sup>a</sup>  $P < .01$  compared with reference levels.

<sup>b</sup>  $P < .005$  compared with reference levels.

<sup>c</sup>  $P < .001$  compared with reference levels.

<sup>d</sup> Indicates maximal improvement after oral theophylline treatment.

<sup>e</sup>  $P < .05$  compared with pretreatment.

<sup>f</sup> Indicates improvement after 4 weeks of intranasal theophylline treatment.

<sup>g</sup>  $P < .005$  compared with before treatment.

<sup>h</sup>  $P < .01$  compared with oral theophylline treatment.

<sup>i</sup>  $P < .001$  compared with before treatment.

<sup>j</sup>  $P < .05$  compared with reference levels.

<sup>k</sup>  $P < .05$  compared with oral theophylline treatment.

tranasal theophylline treatment. After oral theophylline treatment, 6 patients reported overall increased taste and smell function, whereas 4 reported no improvement. After intranasal theophylline treatment, 8 of the 10 patients reported overall improvement in taste and smell functions, whereas 2 reported no improvement. This response frequency is higher than that previously reported among patients with hyposmia and treated with oral theophylline, in which slightly more than 50% reported improvement.<sup>40</sup>

Taste and smell acuity were measured as subjectively improved after oral theophylline treatment, but this improvement was measured as increased after 4 weeks of intranasal theophylline treatment (**Table 3**). After intranasal theophylline treatment, a 2-fold improvement was measured for taste and smell functions compared with oral treatment. Paired  $t$  test results showed that responses after intranasal theophylline were significantly greater than after oral theophylline treatment (taste,  $P < .05$ ; smell,  $P < .025$ ).

Body weight increased from pretreatment levels after oral theophylline treatment, but weight increased more after intranasal theophylline treatment. After oral theophylline treatment, mean (SEM) weight increased by 1.5 (0.4) kg from pretreatment values, whereas after intranasal theophylline treatment, weight increased by 2.5 (0.5) kg from pretreatment values. Patients related this change to increased food flavor obtained by improved smell function after intranasal theophylline treatment, which increased appetite and food enjoyment, resulting in subsequent weight gain. These changes were measured in

each patient group despite no sensory improvement in 4 patients after oral theophylline treatment and none in 2 after intranasal theophylline treatment.

During oral theophylline treatment, the mean (SEM) serum theophylline level at the time of maximum improvement for these 10 patients was 6.4 (2.0) mg/L (to convert to micromoles per liter, multiply by 5.55). During intranasal theophylline treatment, the mean serum theophylline level was 0.0 (0.0). Discontinuation of intranasal theophylline treatment resulted in loss of smell and taste function within 1 week in 2 patients and after 6 weeks in 2. Four patients reported some persistence of improvement after 10 weeks.

#### COMMENT

Results of this open-label, single-source, controlled pilot trial demonstrate that oral theophylline effectively improved hyposmia, as previously reported.<sup>40,42</sup> The earliest this improvement was measured was after 2 months of treatment, but maximal improvement varied from 4 to 12 months. These results also demonstrate that oral theophylline was effective in improving hypogeusia in the same time frame as improvement in smell acuity.

In addition, intranasal theophylline was shown to be safe and more effective than oral theophylline in correcting hyposmia and hypogeusia. This improvement was measured as early as 1 week after starting treatment, but maximal improvement varied from 1 to 4 weeks.

**Table 2. Olfactometry in Patients With Hyposmia and Hypogeusia Before and After Treatment With Oral and Intranasal Theophylline**

| Condition                                                                 | Olfactometry, Mean (SEM)    |                           |                        |            |                           |                            |                          |                          |                             |                             |                        |                        |                             |                             |                           |                        |
|---------------------------------------------------------------------------|-----------------------------|---------------------------|------------------------|------------|---------------------------|----------------------------|--------------------------|--------------------------|-----------------------------|-----------------------------|------------------------|------------------------|-----------------------------|-----------------------------|---------------------------|------------------------|
|                                                                           | Pyridine                    |                           |                        |            | Nitrobenzene              |                            |                          |                          | Thiophene                   |                             |                        |                        | Amyl Acetate                |                             |                           |                        |
|                                                                           | BU, mmol/L                  |                           | %                      |            | BU, mmol/L                |                            | %                        |                          | BU, mmol/L                  |                             | %                      |                        | BU, mmol/L                  |                             | %                         |                        |
|                                                                           | DT                          | RT                        | ME                     | HR         | DT                        | RT                         | ME                       | HR                       | DT                          | RT                          | ME                     | HR                     | DT                          | RT                          | ME                        | HR                     |
| Before treatment                                                          | 8.9<br>(0.7) <sup>a</sup>   | 9.3<br>(0.8) <sup>b</sup> | 16<br>(6) <sup>a</sup> | -14<br>(5) | 9.1<br>(0.7) <sup>a</sup> | 10.1<br>(0.6) <sup>c</sup> | 6<br>(2) <sup>a</sup>    | 3<br>(2)                 | 9.4<br>(0.7) <sup>a</sup>   | 10.2<br>(0.4) <sup>a</sup>  | 10<br>(2) <sup>a</sup> | -3<br>(2) <sup>b</sup> | 9.5<br>(0.7) <sup>a</sup>   | 11.0<br>(0.5) <sup>a</sup>  | 0.6<br>(0.3) <sup>a</sup> | 0<br>(0)               |
| After oral theophylline anhydrous treatment <sup>d</sup>                  | 6.3<br>(0.6) <sup>a,e</sup> | 6.3<br>(0.6) <sup>f</sup> | 25<br>(8) <sup>a</sup> | -24<br>(9) | 5.9<br>(1.0) <sup>g</sup> | 6.5<br>(0.9) <sup>e</sup>  | 23<br>(9) <sup>c</sup>   | 20<br>(10)               | 6.0<br>(0.8) <sup>c,f</sup> | 6.3<br>(1.1) <sup>f,h</sup> | 20<br>(9) <sup>a</sup> | -17<br>(8)             | 5.4<br>(0.9) <sup>i,j</sup> | 6.1<br>(0.9) <sup>h,k</sup> | 21<br>(8) <sup>b,g</sup>  | 20<br>(9) <sup>e</sup> |
| After intranasal theophylline methylpropyl paraben treatment <sup>l</sup> | 5.9<br>(0.8) <sup>a,e</sup> | 6.2<br>(0.9) <sup>g</sup> | 27<br>(7) <sup>a</sup> | -22<br>(7) | 4.2<br>(1.0) <sup>i</sup> | 5.1<br>(1.1) <sup>k</sup>  | 24<br>(7) <sup>c,g</sup> | 21<br>(7) <sup>g,j</sup> | 4.7<br>(1.2) <sup>i</sup>   | 5.8<br>(1.1) <sup>i,j</sup> | 23<br>(7) <sup>a</sup> | -18<br>(9)             | 3.3<br>(0.9) <sup>k</sup>   | 3.3<br>(0.9) <sup>k,m</sup> | 22<br>(7) <sup>b,i</sup>  | 12<br>(8)              |
| Reference level                                                           | 3.7<br>(0.3)                | 6.0<br>(0.7)              | 64<br>(3)              | -20<br>(2) | 3.6<br>(0.4)              | 6.0<br>(0.6)               | 51<br>(4)                | 4<br>(1)                 | 3.2<br>(0.6)                | 3.3<br>(0.5)                | 66<br>(4)              | -13<br>(2)             | 3.1<br>(0.5)                | 3.3<br>(0.6)                | 51<br>(4)                 | 1<br>(1)               |

Abbreviations: See Table 1.

<sup>a</sup>  $P < .001$  compared with reference level.<sup>b</sup>  $P < .005$  compared with reference level.<sup>c</sup>  $P < .01$  compared with reference level.<sup>d</sup> Indicates maximal improvement after oral theophylline treatment.<sup>e</sup>  $P < .05$  compared with before treatment.<sup>f</sup>  $P < .01$  compared with before treatment.<sup>g</sup>  $P < .02$  compared with before treatment.<sup>h</sup>  $P < .02$  compared with reference level.<sup>i</sup>  $P < .005$  compared with before treatment.<sup>j</sup>  $P < .05$  compared with reference level.<sup>k</sup>  $P < .001$  compared with before treatment.<sup>l</sup> Indicates improvement after 4 weeks of intranasal theophylline treatment.<sup>m</sup>  $P < .05$  compared with oral theophylline treatment.**Table 3. Comparison of Quantitative Subjective Changes After Oral and Intranasal Theophylline Treatment in 10 Patients With Hyposmia and Hypogeusia**

| Condition                                                           | Change, %                |       |                          |       |
|---------------------------------------------------------------------|--------------------------|-------|--------------------------|-------|
|                                                                     | Taste                    |       | Smell                    |       |
|                                                                     | Mean (SEM)               | Range | Mean (SEM)               | Range |
| Oral theophylline anhydrous treatment <sup>a</sup>                  | +10.5 (5.6)              | 0-50  | +14.0 (6.3)              | 0-60  |
| Intranasal theophylline methylpropyl paraben treatment <sup>b</sup> | +22.0 (7.8) <sup>c</sup> | 0-80  | +28.0 (8.6) <sup>d</sup> | 0-90  |

<sup>a</sup> Indicates maximal improvement after oral theophylline treatment.<sup>b</sup> Indicates improvement after 4 weeks of intranasal theophylline treatment.<sup>c</sup>  $P < .05$  compared with oral theophylline response.<sup>d</sup>  $P < .025$  compared with oral theophylline response.

Mechanisms by which intranasal theophylline was more effective than oral theophylline are not clearly defined. Intranasal drug delivery avoids the first-pass hepatic effect of an oral drug, bypassing initial cytochrome P450 metabolism and decreasing metabolism of the orally administered drug, thereby allowing for lower intranasally administered drug doses to be clinically efficacious. This lowering of the drug dose from a range of 200 to 800 mg orally to 40 µg intranasally was sufficient and specific enough to also avoid production of systemic adverse effects.<sup>52</sup> This delivery mechanism may also avoid development of drug resistance that has occurred with oral theophylline.<sup>42</sup> In addition, because more drug presumably contacts the olfactory epithelium with intranasal than with oral theophylline, direct nasal stimulation

may activate more olfactory receptors than does oral administration.

However, additional actions of intranasal theophylline might enhance its therapeutic efficacy. Theophylline has been shown to inhibit symptoms of allergic rhinitis,<sup>53,54</sup> which affected 3 patients in the intranasal trial. Many of the diseases and conditions that caused hyposmia and hypogeusia have an associated inflammatory component that may be suppressed by the anti-inflammatory effects of a phosphodiesterase inhibitor.<sup>54,55</sup> In addition, drugs introduced intranasally can be delivered into the brain (1) directly by absorption through the cribriform plate along the olfactory bulb,<sup>56-60</sup> (2) indirectly by absorption through blood-brain barrier receptors,<sup>61-63</sup> or (3) through combinations of both methods. Although stud-

ies of theophylline absorption from nasal mucus into the brain have not been performed, studies of insulin,<sup>58,66</sup> nerve growth factor,<sup>58</sup> several neurotransmitters,<sup>67,68</sup> and other moieties<sup>37,60,69,70</sup> indicate uptake of these intranasally introduced moieties into the brain.<sup>71</sup>

Whatever its mechanism of action, intranasal theophylline in this pilot study corrected hyposmia and hypogeusia relatively rapidly in 8 of 10 patients with several clinical diagnoses. The 2 patients who did not experience improvement were men, one with allergic rhinitis and the other with the effects of viral illness.

These results are consistent with prior studies in which several intranasal drugs were more effective than oral drugs. Inhaled adrenocorticosteroids were more effective with fewer adverse effects for asthma treatment than oral adrenocorticosteroids,<sup>72</sup> and inhaled adrenocorticosteroids were more efficacious in asthma treatment than oral prednisolone acetate.<sup>73</sup> Intranasal zolmitriptan achieved faster control of migraine headaches with fewer effects than the orally administered drug.<sup>74</sup> Nasal administration of chicken type II collagen suppressed adjuvant arthritis in rats more effectively than oral administration.<sup>75</sup>

However, intranasally administered drugs have also been reported to be only as effective as these same drugs given orally. Intranasal estradiol valerate was as effective as oral administration in alleviating postmenopausal symptoms but produced less frequent mastalgia and uterine bleeding.<sup>76</sup> Intranasal desmopressin acetate was as effective for nocturnal enuresis as the oral drug but at a dose one-tenth that of the oral drug.<sup>77</sup> Intranasal desmopressin is the preferred route for management of central diabetes insipidus.<sup>78</sup>

At present, no generally clinically accepted method of treatment for hyposmia and hypogeusia exists. This pilot study suggests a simple, direct, and safe method to improve hyposmia and hypogeusia in a varied group of patients with both dysfunctions. However, this study has limitations. It was designed primarily to determine the safety of intranasal theophylline administration. Although results of its use compared with no treatment and treatment with oral theophylline demonstrate significant sensory improvement, results have to be considered with this intent in mind. Despite these detailed subjective, gustometric, and olfactometric improvements, this study was performed in only 10 subjects without placebo controls. These results, although useful, require repeated performance in larger numbers of patients with placebo controls during a longer treatment period to confirm efficacy. However, we systematically studied this group of 10 patients who served as their own controls throughout each study condition, and hyposmia and hypogeusia improved and weight increased after each treatment condition. In conclusion, intranasal theophylline treatment was safe and effective in improving hyposmia and hypogeusia and was more efficacious than oral theophylline treatment.

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