**Effects of Pentoxifylline on Olfactory Sensitivity**

*A Postmarketing Surveillance Study*

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**Objective:** To investigate the effect of pentoxifylline, an unspecific phosphodiesterase inhibitor, on olfactory function.

**Design:** Longitudinal study.

**Patients:** Nineteen patients who received pentoxifylline to treat inner-ear conditions.

**Main Outcome Measures:** Evaluation of olfactory function (i.e., odor threshold, odor discrimination, and odor identification) before and after administration of pentoxifylline and assessment of nasal airflow.

**Results:** Administration of pentoxifylline had no significant effect on nasal airflow \((P=0.84)\). After administration of pentoxifylline, patients demonstrated a decrease in odor threshold toward lower odor concentrations \((P=0.01)\). The odor threshold shift after administration of pentoxifylline was more pronounced in younger patients than in older patients (correlation between age and change in odor threshold: \(r=-0.72; P=0.001\)). No such changes were observed for suprathreshold olfactory tasks (odor discrimination and odor identification). Six of the 19 patients were found to have hyposmia. Two patients demonstrated a clinically significant decrease in odor threshold after drug administration.

**Conclusions:** The present findings may indicate a role for pentoxifylline in the treatment of olfactory loss. Double-blind, placebo-controlled studies are needed to verify whether pentoxifylline can improve olfactory sensitivity in patients with olfactory disorders.


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**THE ESTIMATED PREVALENCE** of olfactory disorders in the general population is 20%, and approximately 5% of individuals have functional anosmia. Problems with cooking and mood changes are the most frequently reported dissatisfaction that lead to a substantial decrease in quality of life in patients with loss of the sense of smell. Although several studies have been performed, to date, there has been no conservative therapy for loss of smell that provides a long-lasting effect. This clearly suggests the rationale for new therapeutic approaches.

Signal transduction starts when an odor molecule binds at receptors of an olfactory sensory neuron. The odor-receptor complex leads to intracellular activation of type III adenylate cyclase via a G protein. This results in increased intracellular concentration of adenosine 3’5’-cyclic monophosphate (cAMP). An elevated intracellular cAMP level causes calcium influx and ensuing depolarization of the neuron. cAMP is metabolized by phosphodiesterases (PDEs). In the cilia of olfactory sensory neurons, cAMP is degraded by a calcium/calmodulin-dependent PDE (also called PDE1C2). Because pentoxifylline is an unspecific PDE inhibitor, the rationale behind the present study was that pentoxifylline-induced inhibition of PDE1C2 could result in increased intracellular concentration of cAMP. This elevated cAMP level could lead to increased response of olfactory sensory neurons to chemical stimuli, which in turn could have an effect on human olfactory sensitivity. This theoretical approach is supported by alterations in electro-olfactograms reported in PDE1C knock-out mice. In addition, theophylline (a methylxanthine derivative like pentoxifylline) is used at least in 1 clinic in the treatment of olfactory disorders, although no reliable effect has been demonstrated. In a postmarketing surveillance study, we investigated whether pentoxifylline leads to changes in olfactory sensitivity in patients who receive the medication to treat inner-ear dysfunction.
The prospective postmarketing surveillance study was performed according to the Declaration of Helsinki guidelines on biomedical research involving human subjects. All 19 patients were given pentoxifylline to treat inner ear dysfunction such as sudden hearing loss and tinnitus to improve microcirculation of blood in the cochlea. The indication for medical therapy was set according to the suggestions of the German Society for Otorhinolaryngology, Head and Neck Surgery, for treatment of sudden hearing loss or tinnitus. Patients with acute or chronic rhinosinusitis were not included in the study. Patients were recruited from our outpatient department and were treated as outpatients in our daycare clinic or as inpatients.

Fifteen patients received intravenous pentoxifylline (Pentoxifyllin; ratiopharm GmbH, Ulm, Germany), 200 mg, dissolved in 500 mL of 0.9% sodium solution (E154; Serumwerke Bernburg AG, Bernburg, Germany) twice daily, infused for 2 hours. Four patients received oral pentoxifylline (Ralofekt; Temmler Pharma GmbH & Co KG, Marburg, Germany), 200 mg, 3 times daily.

SELF-ASSESSMENT OF OLFACTORY SENSITIVITY

Before olfactory testing was performed, each patient was asked to evaluate his or her olfactory function as very good, good, normal, poor, very poor, or complete loss. Before the second olfactory test was performed, patients were asked to indicate a possible change in olfactory sensitivity as better, unchanged, or worse compared with olfactory function at the first visit. Furthermore, they were asked about the presence of parosmia or phantosmia. In a longitudinal study, olfactory function was assessed 1 to 2 hours before administration of the first dose of pentoxifylline and on a different day 1 to 2 hours after administration of pentoxifylline. In individual patients, measurements were performed at approximately the same time of day to account for possible diurnal changes in the sense of smell. A relatively short test-retest interval was chosen to reduce the number of dropouts.

OLFACTORY TESTING

For assessment of olfactory function, an odor-identification kit (Sniffin’ Sticks penlike odor-containing devices; Burghart Medical Technology, Wedel, Germany) was used. This kit is comprised of 3 tests of olfactory function, that is, tests for odor threshold, odor discrimination, and odor identification. Odor threshold was determined for phenyl ethyl alcohol using a 3-alternative forced-choice task. Three pens were presented to the patient in random order; 1 contained the odorant at 1 of 16 possible dilutions and the other 2 contained solvent only. The patient’s task was to determine which of the 3 pens smelled of the odorant that had been presented at the beginning of the test as the highest of the 16 concentrations. Using a staircase paradigm, triplets of pens were presented to the patient every 20 to 30 seconds. Subjects were blindfolded to prevent visual identification of the odor-containing pens. Correct identification of the pen that contained the odorant in 2 successive trials triggered a reversal of the staircase to the next lower concentrations, whereas a single incorrect identification triggered the reversal of the staircase to the next higher concentration. From a total of 7 reversals, the mean of the last 4 staircase reversal points was used as the threshold estimate. Odor discrimination was tested using 16 triplets of odorants. Patients were presented with 3 pens, 2 containing the same odorant and 1 containing a different odorant. The patient’s task was to identify the pen that smelled different; thus, again a 3-alternative forced-choice test design was used. Subjects were blindfolded to prevent visual detection of the target odor pens. They were allowed to sample each odor only once. The interval between presentations of odor triplets was at least 30 seconds. The interval between presentations of individual odorant pens was approximately 3 seconds. For odor identification, 16 odorants were presented in random sequence. The patients were free to sample the odors as often as necessary to identify them from a list of 4 descriptors. The experimenter presented odor-containing pens at an interval of at least 30 seconds to prevent olfactory desensitization.

For a more comprehensive analysis of the results, data from the 3 tests, phenyl ethyl alcohol odor threshold (T), odor discrimination (D), and odor identification (I) were summed to a composite score, the so-called TDI score.

ANTERIOR RHINOMANOMETRY

Because odor threshold is intimately linked to nasal airflow and pentoxifylline as an unspecific phosphodiesterase inhibitor could effect nasal patency, nasal airflow was evaluated. After olfactory tests were completed, nasal airflow was assessed using anterior rhinomanometry (Rhinosoft; Hortmann, Münster, Germany) separately on each side. Transnasal differential pressure and concurrent nasal airflow are measured when specific nasal breathing is used. Nasal airflow in milliliters per second was obtained when the transnasal differential pressure was 150 Pa. Total nasal airflow was calculated by summing nasal airflow in the left and right nostrils.

STATISTICAL ANALYSES

We tested the effect of pentoxifylline on olfactory sensitivity. The primary outcome measure insofar as efficacy of pentoxifylline was the percentage of patients with an increase of 3 points in the TDI score. The assumed standard deviation of the change in the TDI score was 4. Using 0.8 power to detect a significant difference (P= .05, 1-sided), 13 patients were required.

Data were evaluated using commercially available software (SPSS for Windows, version 12.0; SPSS Inc, Chicago, Illinois). We used t tests for paired samples to compare results from different test sessions. Statistical significance was set at α < .05.

RESULTS

Nineteen patients (10 women and 9 men; mean [SD] age, 51 [19.9] years) were recruited between January 1 and October 31, 2006. Cause of olfactory dysfunction, comorbid conditions, and medications are given in the Table. Six patients were found to have hyposmia (TDI score < 30). All patients were unavailable for follow-up.

All patients but 1 evaluated their sense of smell as normal, good, or very good. One patient assessed his olfactory function as poor; his TDI test score indicated hyposmia. No patients demonstrated any change in olfactory function or reported parosmia or phantosmia after administration of pentoxifylline. Total nasal airflow did not change after administration of pentoxifylline (mean [SD], 853 [355] mL/s before and 873 [311] mL/s after drug administration; P = .84). The mean (SD) interval between the 2 tests was 2.4 (1.4) days.

After drug administration, a mean (SD) increase of 2.9 (5.0) points on the TDI score was observed (P = .08). Scores for the 2 olfactory tests of suprathreshold olfactory function (odor identification and odor discrimination...
tion) did not change significantly after drug administration ($P = .87$ and $P = .50$, respectively). However, odor threshold decreased significantly (mean [SD], 1.2 [1.9]; $P = .01$; Figure 1) after administration of pentoxifylline. Analysis of the influence of patient age on changes in odor threshold after drug administration indicated a pronounced change in younger patients compared with older patients ($r = -.72; P = .001$; Figure 2). In the 6 pa-

### Table. Patient Data

<table>
<thead>
<tr>
<th>Patient No. /Sex/Age, y</th>
<th>Cause of Olfactory Dysfunction</th>
<th>Comorbid Conditions</th>
<th>Concurrent Medication</th>
<th>Route of Administration of Pentoxifylline</th>
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<tbody>
<tr>
<td>1/F/87</td>
<td>Not known</td>
<td>Hypertension, arthrosis</td>
<td>Losartan potassium, 50 mg/d; carvedilol, 6.25 mg twice daily; prednisolone, 5 mg/d</td>
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<td>None</td>
<td>None</td>
<td>PO</td>
</tr>
<tr>
<td>3/F/67</td>
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<td>None</td>
<td>None</td>
<td>IV</td>
</tr>
<tr>
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<td>None</td>
<td>None</td>
<td>IV</td>
</tr>
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<td>Insulin (Actraphane), 10:10.0 IU; insulin (Protaphane), 0:0:20 IU; pravastatin sodium, 10 mg/d; ramipril, 1.25 mg/d; amiodarone hydrochloride, 200 mg/d</td>
<td>IV</td>
</tr>
<tr>
<td>6/M/51</td>
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<tr>
<td>7/M/59</td>
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</tr>
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<td>None</td>
<td>IV</td>
</tr>
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<td>IV</td>
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<td>IV</td>
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<tr>
<td>19/M/19</td>
<td>Noise trauma</td>
<td>None</td>
<td>None</td>
<td>IV</td>
</tr>
</tbody>
</table>

Abbreviation: IV, intravenous; PO, oral.

Figure 1. Box plots of odor threshold in patients before and after administration of pentoxifylline. An odor threshold of 1 indicates the highest investigated concentration of phenyl ethyl alcohol, and 16 indicates the 16-fold diluted concentration. The boundary of the boxes closest to zero indicates the 25th percentile; a line within the box marks the median; and the boundary of the box farthest from zero indicates the 75th percentile. Whiskers above and below the box indicate the 90th and 10th percentiles, respectively. The asterisk indicates a significant difference between measurements 1 and 2.

Figure 2. Scatterplot of changes in odor threshold (in dilution steps) after administration of pentoxifylline according to age. Positive values of change in odor threshold indicate decreased odor thresholds toward lower odor concentrations at the second test.
patients who tested positive for hyposmia, the TDI score increased nonsignificantly (P = .07) by a mean (SD) of 5.62 (6.02) points; however, odor threshold decreased significantly (P = .007) by 2.46 (1.35) dilution steps after drug administration. In the 1 patient who reported poor olfactory function and who tested positive for hyposmia, the TDI score decreased by 0.25 points after administration of pentoxifylline.

Three men (ages 25, 31, and 39 years) and 1 woman (age 56 years) received medication orally. Among them, odor threshold decreased in the 2 youngest patients by 2.75 and 4.0 dilution steps, respectively, and increased in the 2 older patients by 1.5 and 0.25 dilution steps, respectively.

The present study provided the following major results: (1) pentoxifylline led to a decreased odor threshold resulting in increased olfactory sensitivity and (2) the odor threshold shift seems to be age dependent and is more pronounced in younger patients. Olfactory testing using Sniffin’ Sticks demonstrated a slight but nonsignificant increase in the TDI score after drug administration. However, when analyzing the 3 subtests of the Sniffin’ Sticks test battery separately, a significant decrease was found for odor thresholds; however, no similar increase in sensitivity was observed for suprathreshold olfactory tasks. Odor thresholds decreased significantly by a mean (SD) of 1.2 (1.9) dilution steps in the 19 patients, which is not explained by repeated testing.23 Six patients (32%) tested positive for hyposmia, which reflects approximately the prevalence of hyposmia in the German population.1 In these 6 patients, the mean (SD) TDI score increased by 5.62 (6.02) points and odor threshold decreased by 2.46 (1.35) dilution steps. Glucocorticoid therapy can temporarily improve olfactory function in patients with sinonasal cause of olfactory dysfunction.27,28 In a study by Blomqvist et al,22 in patients with olfactory dysfunction, odor thresholds improved significantly after 10 days of combined oral and nasal glucocorticoid therapy. The mean odor threshold shift in their study was 3 dilution steps (no standard deviation reported), comparable to the 2.46 dilution steps we found in our patients with hyposmia. Clinically significant improvement in olfactory function is reported when odor threshold decreases by 2.5 dilution steps.21 Thus, 2 of our 6 patients with hyposmia demonstrated clinically significant improvement in olfactory sensitivity after drug administration.

Analysis of the effect of patient age on changes in odor threshold after drug administration revealed a significantly pronounced change in younger patients compared with older patients (r = -.72; P = .001). Change in olfactory thresholds was not observed in patients older than 70 years. Inasmuch as olfactory deficits frequently become obvious at this age,20 it might be hypothesized that, in older subjects, olfactory sensory neurons have already degenerated to a certain degree, resulting in inefficiency of pentoxifylline to increase olfactory sensitivity, probably by inhibition of PDE1C2.23 An age-dependent effect of pentoxifylline was also found in human cerebral blood flow and in vertebrate pulmonary blood flow, indicating that age-dependent physiologic changes might be responsible for the observed age-related effect of pentoxifylline on olfactory sensitivity.24-26

All patients evaluated their sense of smell as normal or better than normal except 1 patient who indicated poor olfactory function. Although some patients demonstrated a clinically significant increase in olfactory sensitivity, no patient reported a change in olfactory function after treatment with pentoxifylline. Self-rating of olfactory function is unreliable.27 Especially in patients with subjectively normal olfactory function, relatively large changes in olfactory sensitivity are often not noticed,28,29 whereas improvement would be indicated by most patients with olfactory loss.30 It seems that, in patients with subjectively normal olfactory function, odor threshold must decrease severely before it is noticed. To our knowledge, there are no data about the degree to which odor threshold must decrease in patients with normosmia to be noticed as an improvement in olfactory sensitivity.

The 1 patient who reported poor olfactory sensitivity tested positive for hyposmia. His TDI score decreased by 0.25 points after administration of pentoxifylline. This might explain why he did not notice any change in olfactory sensitivity.

Four patients received medication orally. Although the bioavailability of pentoxifylline is reduced by 30% to 40% after oral administration, 2 patients who received oral medication demonstrated a clinically significant decrease in odor threshold.

The background for the present study was whether pentoxifylline could be useful in the treatment of olfactory dysfunction. In a pilot study such as this, however, it should be explored first whether patients with subjectively normal olfactory function (who received pentoxifylline to treat another cause) would demonstrate a change in olfactory sensitivity. To this end, patients were studied who received pentoxifylline according to the suggestions of the German Society for Otorhinolaryngology, Head and Neck Surgery, about treatment of sudden hearing loss or tinnitus. Among the studied patients, we expected the reported prevalence of hyposmia and anosmia to be similar to that in the general population.1 Thus, we were able to study the effect of pentoxifylline in 6 patients with hyposmia and 13 with normal olfactory function. Only a double-blind placebo-controlled trial can determine whether pentoxifylline can improve olfactory sensitivity in patients with olfactory loss. For such a study, 40 patients with reduced olfactory sensitivity should be included to detect clinically significant improvement of 5.5 points in the TDI score. Before initiating such a complex and costly study, our objective was to determine whether pentoxifylline can affect olfactory sensitivity.

In conclusion, pentoxifylline led to encouraging improvement in olfactory sensitivity by up to 4 dilution steps in younger patients, and 33% of patients with hyposmia demonstrated clinically significant improvement in olfactory function. A double-blind, placebo-controlled trial is necessary to confirm whether pentoxifylline can improve olfactory function in patients with olfactory dysfunction.
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Author Contributions: Dr Gudziol had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Gudziol and Hummel. Acquisition of data: Gudziol. Analysis and interpretation of data: Gudziol and Hummel. Drafting of the manuscript: Gudziol and Hummel. Critical revision of the manuscript for important intellectual content: Gudziol and Hummel. Statistical analysis: Gudziol and Hummel. Obtained funding: Hummel. Administrative, technical, and material support: Gudziol and Hummel. Study supervision: Hummel. Financial Disclosure: None reported.

REFERENCES


