Topical Ephedrine Administration and Nasal Chemosensory Function in Healthy Human Subjects

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Objective: To investigate dose-related effects of ephedrine on olfactory function in healthy subjects.

Design: Placebo-controlled, randomized, double-blind study.

Methods: Drug effects were assessed using olfactory and trigeminal psychophysical measures (intensity ratings, odor discrimination, butanol and formic acid thresholds); nasal patency was assessed by means of anterior rhinoresistometry. The investigation was performed in 24 healthy volunteers; subjects were assigned to treatments A, B, or C (3 groups with 8 subjects each; 4 women and 4 men per group). All subjects received either placebo or ephedrine in both nostrils; group A subjects received placebo, and group B and C subjects received ephedrine in dosages of 0.12 and 0.24 mg, respectively.

Results: Treatment with ephedrine produced a tendency toward an increase of nasal airflow. However, during the time of observation there was no significant difference between effects produced by the 2 dosages. Ephedrine had no systematic effect on measures of olfactory function. The only significant correlation to the nasal airflow was found for perceived intensity of the trigeminal stimuli, which increased with increasing flow.

Conclusions: Ephedrine appeared to have neither negative nor major positive effects on intranasal chemosensory function in healthy subjects. This indicates that ephedrine may be used as a decongestant in studies on olfaction.


Ephedrine is routinely used in the treatment of acute rhinitis and sinusitis and in examinations of the nose as a topical decongestant. It is an α- and β-adrenergic agonist that may also enhance release of norepinephrine. Similar to other decongesting agents, it has been shown to significantly reduce congestion of the nasal cavity when applied intranasally. Ephedrine is also known for its relatively short duration of action, which may last 3 to 6 hours. Like other over-the-counter medications for the treatment of nasal congestion, this drug is used extensively. However, so far no systematic study has investigated its effects on human chemosensory function. In addition, it is unclear whether ephedrine itself produces olfactory dysfunction. Such possible side effects might be due, for example, to either direct toxic effects of the administered spray or the decreased mucosal blood flow itself, which in turn might interfere with inflammatory defense mechanisms, leaving the mucosa relatively less well protected.

Thus, we tried to find an answer to the question of whether ephedrine influences olfactory and trigeminal sensitivity in healthy subjects.

RESULTS

Administration of ephedrine resulted in a tendency toward higher nasal airflows ($F = 3.03$, $P = .07$). Saline placebo produced a mean increase of flow by 3%, single administration of ephedrine (0.12 mg) increased the flow by approximately 9%, 2 sprays (0.24 mg) increased the flow by approximately 5%.

None of the measures of intranasal chemosensory function was affected by administration of ephedrine or placebo (odor discrimination: $F = 0.78$, $P = .47$; odor threshold: $F = 0.73$, $P = .49$; trigeminal threshold: $F = 1.87$, $P = .18$; trigeminal intensity ratings: $F = 0.78$, $P = .47$). The subjects' ability to identify odors was found to be identical before and after drug administration (Table).

A significant correlation between measures of intranasal chemosensory function and nasal airflow was only observed for intensity ratings of formic acid ($r_{24} = 0.48$, $P = .02$, Figure).

COMMENT

This study provided the following major findings: (1) Ephedrine produced a tendency toward an increase of nasal airflow,
SUBJECTS, MATERIALS, AND METHODS

The study was designed as a placebo-controlled, randomized, double-blind investigation. It was performed according to the Declaration of Helsinki on biomedical research (Tokyo amendment). Subjects gave written informed consent. A total of 24 volunteers participated (12 women and 12 men; mean age, 27 years [range, 21-35 years]). The mean weight was 65 kg (range, 55-92 kg) and mean height was 171 cm (range, 159-191 cm). All subjects were in excellent health as established by a thorough physical examination and a detailed history. None of the subjects had acute rhinitis or a history of chronic nasal disease. None of the subjects took any medication except for contraceptives. Subjects were advised to not drink alcohol on the evening before commencement of measurements, to get sufficient sleep, and to not eat or smoke or drink anything other than water 1 hour before measurements.

Before the session, subjects were acquainted with the experimental procedures. To control possible circadian influences, all sessions took place at the same time of day (±2 hours). The whole testing procedure lasted about 120 minutes.

Subjects were randomly assigned to treatments A, B, or C (3 groups with 8 subjects each, consisting of 4 women and 4 men). Two sprays each of either placebo or ephedrine were applied to the left and right nostrils 15 minutes before the second session started (baseline measurement was the first session). Subjects in group A received placebo, group B and C subjects received ephedrine in dosages of 0.12 mg and 0.24 mg, respectively; the dosages compared with those recommended with common decongestants.

Active anterior rhinoresistometry was assessed by means of a computer-assisted online system (Rhinoresistometer model RRM 1000; Stimotron Medizinische Geräte GmbH, Leipzig, Germany). Sponge nozzles were used to keep the pressure measuring tube in place. A small, transparent anesthetic-type mask was used. The rhinomanometer was routinely calibrated every day before the first measurement. Recording was performed in sitting subjects while they were breathing in a slow, regular fashion.

Psychophysical testing of olfactory function was performed by means of penlike odor-dispensing devices (Sniffin’ Sticks). Odor identification was assessed using 16 different odors. Subjects had to identify the odor using a multiple-choice form with 4 items. Odor discrimination was performed for 16 triplets of odorants. While 2 pens of each triplet contained the same odorant, subjects had to determine which of the 3 pens smelled different. Odor thresholds were assessed for butanol, dilutions in water were established with a ratio of 1:2 starting at a 4% solution. Using a triple-forced-choice paradigm, thresholds were determined by means of a single staircase method. Similar to the odor discrimination task, 3 odor pens were presented to the subjects, 2 of which contained solvent and the other the odorant in a certain dilution. Subjects then had to indicate the pen that smelled different. Triplets were presented in ascending concentrations approximately every 20 seconds, until subjects had correctly identified the odorant in 2 successive trials. This triggered a reversal of the staircase. Then odors were presented in descending concentrations until the odor was no longer identified. From a total of 7 reversal points, the mean of the last 4 reversals was used as the threshold. Subjects received no immediate feedback regarding the accuracy of their decision.

Intranasal trigeminal sensations were examined by the filter paper strip method introduced by Roseburg et al, using formic acid. As with butanol thresholds, thresholds for formic acid were assessed by means of a single staircase. However, formic acid was presented on filter paper soaked with different concentrations of formic acid dissolved in water. Eight dilutions of formic acid were presented. The lowest concentration was 0.098% vol/vol, the highest concentration was 12.5% vol/vol.

Intensity ratings of formic acid were performed in relation to the subjects’ thresholds; that is, subjects rated the intensity of formic acid solutions 4 times the concentration for which thresholds had been established. Subjects used visual analog scales of 10-cm length. The left-hand end was defined as “no sensation,” and the right-hand end as “extremely intense sensation.”

Statistical analyses were performed by means of SPSS for Windows 8.0 (SPSS Inc, Chicago, Ill). For data normalization, differences were computed between measurements performed after drug administration and at baseline. All parameters were submitted to analyses of variance (between-subject factor “drug” df = 2/21) with Bonferroni post hoc multiple comparisons. In addition, Pearson correlational analyses were performed to examine whether measures of chemo-sensory function changed in relation to changes of nasal airflow. The α level was set at .05.

Although this increase is clinically not relevant, because it is a change below 30%, (2) Ephedrine did not significantly change olfactory or trigeminal function as assessed by means of odor identification, odor discrimination, butanol and formic acid thresholds, and intensity ratings of trigeminal stimuli. (3) Of all measures of intranasal chemosensory function, only intensity ratings of formic acid stimuli were correlated with measures of nasal airflow.

Administration of ephedrine produced a tendency toward an increase in nasal airflow (P = .07). However, the higher dose did not produce a larger effect than a single spray of ephedrine. One reason for this finding may be the short observation period. If it had been longer, it may be assumed that the effect of the lower dose of ephedrine might have worn off earlier than that of the higher dosage. Another reason might simply be found in a ceiling effect present at a dosage of 0.12 mg. Also, as none of the subjects had any mucosa-related problem, this ceiling might have been reached with a lower dose than, for example, in patients with nasal sinus disease.

Despite the effect on nasal airflow, ephedrine had no effect on chemosensory function. Only formic acid intensity ratings exhibited a correlation with nasal airflow. These results compare with recent findings reported by Hummel et al using oxymetazoline as the decongestant. Why was that so? It appears that the improved patency of the nasal cavity itself might have contributed to the increase in the ratings. It has been shown in a controlled study that external nasal dilators affect odor intensity rating; this was interpreted in terms of a “perceptual constancy model,” where a decrease in nasal resistance decreases perceived sniff vigor, which in turn produces an increase in perceived odor intensity. This may also apply to the use of na-
Results of Assessments Before and After Drug Administration in Placebo and Ephedrine Groups*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n = 8)</th>
<th>0.12-mg Ephedrine (n = 8)</th>
<th>0.24-mg Ephedrine (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>16 (0)</td>
<td>16 (0)</td>
<td>16 (0)</td>
</tr>
<tr>
<td>After</td>
<td>16 (0)</td>
<td>16 (0)</td>
<td>16 (0)</td>
</tr>
<tr>
<td>Discrimination†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>14.6 (0.3)</td>
<td>14.8 (0.2)</td>
<td>12.4 (0.4)</td>
</tr>
<tr>
<td>After</td>
<td>14.6 (0.3)</td>
<td>14.8 (0.2)</td>
<td>12.9 (0.3)</td>
</tr>
<tr>
<td>Olfactory threshold†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>13.5 (0.5)</td>
<td>13.3 (0.4)</td>
<td>13.3 (0.8)</td>
</tr>
<tr>
<td>After</td>
<td>13.5 (0.4)</td>
<td>13.4 (0.4)</td>
<td>13.8 (2.9)</td>
</tr>
<tr>
<td>Trigeminal threshold†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>7.5 (0.2)</td>
<td>7.5 (0.2)</td>
<td>7.5 (0.2)</td>
</tr>
<tr>
<td>After</td>
<td>7.4 (0.2)</td>
<td>7.9 (0.1)</td>
<td>7.6 (0.2)</td>
</tr>
<tr>
<td>Intensity rating‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>85.5 (2.0)</td>
<td>86.0 (2.3)</td>
<td>82.9 (2.9)</td>
</tr>
<tr>
<td>After</td>
<td>87.8 (1.7)</td>
<td>90.9 (1.5)</td>
<td>85.6 (2.1)</td>
</tr>
<tr>
<td>Nasal airflow, cm3/s§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>1129 (44)</td>
<td>1261 (59)</td>
<td>1143 (60)</td>
</tr>
<tr>
<td>After</td>
<td>1160 (50)</td>
<td>1368 (49)</td>
<td>1205 (60)</td>
</tr>
</tbody>
</table>

* Data are given as mean (SE).
† See “Materials and Methods” section for explanation of measurements.
‡ Measured in estimation units.
§ Measured by rhinorhymosiontometry.

Correlation between intensity ratings of trigeminal stimuli (measured in estimation units) and nasal airflow (measured by rhinorhymosiontometry). Intensity ratings and nasal airflow data were normalized (difference between measurements obtained after drug administration and at baseline). A significant correlation was found \( r^2 = 0.48, P = .02 \).

Ephedrine exerted no dose-related changes on chemosensory functions, although it increased nasal volume. As this study was performed in healthy subjects with little mucosal discharge, it can be assumed that ephedrine had access to large portions of the olfactory epithelium. However, studies performed by means of gamma-camera scans and endoscopic photography indicate that even in healthy subjects a large portion of a nasal spray is deposited in the anterior nasal cavity.

In conclusion, this study revealed that ephedrine has neither negative nor major positive effects on intranasal chemosensory function. Therefore, this drug appears to be suited as a decongestant for studies on olfaction.

Accepted for publication March 11, 1999.

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REFERENCES