

Intranasal Administration of Drugs

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Objective: To investigate how nasally applied substances distribute in the nose depending on the form of application.

Design: Observer-blinded study.

Setting: University hospital research unit.

Participants: Fifteen healthy volunteers aged 22 to 32 years.

Interventions: Forms of application included (1) nasal drops applied with a pipette, (2) nasal spray, and (3) a system producing squirts. Blue food dye was used to visualize the intranasal distribution of the liquid. The investigation was performed using nasal endoscopy.

Main Outcome Measure: Intranasal distribution of the dye was judged by 2 independent observers blinded to the applicator system used.

Results: The nasal drops predominantly reached the nasal floor. The nasal spray was widely distributed in the nasal mucosa; however, most of it was intercepted by the middle turbinate and did not reach the olfactory cleft effectively. Using the squirt system, the olfactory cleft was reached in most participants.

Conclusions: Previous failure of therapy with locally applied drugs in the case of sinonasal smell disorders may be partly due to the fact that the drugs did not reach the olfactory cleft when using traditional forms of application (ie, sprays). However, using an applicator producing squirts seems likely to present the drugs more effectively to the olfactory epithelium. Thus, it may be hypothesized that therapy could be more effective using a squirt system.

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APPROXIMATELY 5% OF THE population exhibits complete anosmia.^{1,2} The prevalence of olfactory impairment in older adults is 25%.³ Sinonasal diseases are the most frequent cause of olfactory disorders (72%), followed by postinfectious olfactory loss (11%), idiopathic causes (6%), head trauma (5%), iatrogenic causes (3%), toxic effects (2%), and congenital anosmia (1%).⁴

In the case of sinonasal olfactory dysfunction, conservative treatment is possible. Many patients with sinonasal hyposmia or anosmia benefit from treatment with oral corticosteroids.⁵⁻⁸ Sinonasal olfactory loss is caused by mechanical obstruction (eg, polyps), whereby odorants cannot access the olfactory epithelium, and inflammation of the olfactory epithelium due to allergic⁹ or nonallergic rhinitis and chronic sinusitis.¹⁰ In the case of nasal polyps, surgery can abolish the mechanical obstruction, but often it has only a limited effect on olfactory dysfunction. It has been suggested that mucosal inflam-

mation seems to affect olfactory function more than nasal obstruction. In fact, in most cases, improvement of olfactory function seems to relate to the anti-inflammatory actions of corticosteroids.¹¹⁻¹³ Details of the mechanism of improvement in olfaction are not fully understood, but systemic corticosteroids are helpful in patients without nasal obstruction due to polyps or obvious inflammatory changes.⁶

A major problem of conservative treatment of sinonasal olfactory loss is that often olfactory function is highly connected to the actual intake of the drugs. Reduction of the dose is frequently paralleled by a reduction in olfactory acuity. Because long-term systemic treatment with corticosteroids negatively affects the risk to benefit ratio, systemic administration is usually changed to local therapy with corticosteroids, mostly administered as sprays. However, few patients benefit from intranasal drug application.^{5,6,14} The reason for this therapeutic failure may partly be due to the spray not reaching the olfactory epithelium. The olfactory mucosa is found only in an area

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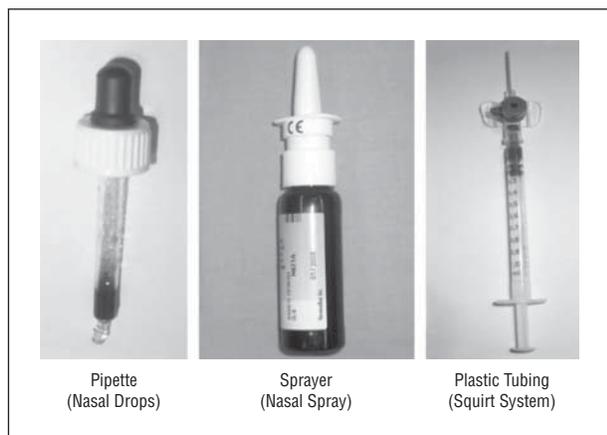


Figure 1. The 3 application forms used were nasal drops applied with a pipette, nasal spray, and a system producing squirts.

at the top of the nasal cavity on both sides, where it reaches from the insertion of the middle turbinate up to the cribriform plate, the superior turbinate, and the opposite septum.¹⁵ Thus, most of the olfactory mucosa is located in a cleft that is only a few millimeters wide and, on average, approximately 7 cm from the nostrils. Consequently, the poor response to treatment with topical corticosteroids is thought to be due to the deposition pattern of the applied drug, which is filtered out already in the anterior portion of the nasal cavity.

Until now, there has been little information about appropriate techniques for the application of drugs to the olfactory cleft. As suggested in a recent review,¹⁶ even when using different methods of application, intranasally applied liquids did not reach the olfactory cleft. When nasal drops are applied with the head in a reclined position, the liquid reaches only the nasal floor. When the head is bent over the edge of the bed, the lower part of the middle turbinate is reached; a similar situation is present when the Mecca position is used.

This situation demands the development of strategies to improve the local application of nasal drugs in the case of olfactory dysfunction due to sinonasal disease. If it would be possible to treat sinonasal olfactory disorders effectively, approximately three-fourths of all patients with olfactory loss could have a better quality of life. Thus, the aim of the present study is to investigate, as a first step, how nasally applied substances distribute in the nose depending on the form of application and how they may be applied most effectively to the olfactory cleft. Based on preliminary experiments with squirt guns, it was hypothesized that squirts of the liquid would have the highest chance of reaching the olfactory cleft.

METHODS

Fifteen young healthy volunteers participated (5 men and 10 women; age range, 22-32 years). None of them reported nasal problems, such as acute rhinitis, obstruction, or acute allergies. Participants were given detailed information about all the testing procedures, and written informed consent was provided by all the participants before the study. All the experiments were performed according to the Declaration of Helsinki. The study design was approved by the ethics committee

of the University of Dresden Medical School. Each participant underwent nasal endoscopy by an ears, nose, and throat specialist (M.S.) to preclude nasal abnormalities.

Three different application forms were investigated: (1) nasal drops applied with a pipette, (2) nasal spray, and (3) a system producing squirts (**Figure 1**). The squirt system was a sterile plastic tube attached to a syringe. Using these 3 different application forms, water stained with blue food dye was applied to the nasal cavity. The consecutive blue staining of the nasal mucosa permitted visualization of the intranasal distribution of the liquid. The sequence of testing of the 3 different application forms was randomized across all the participants. The 3 techniques were applied in a randomized order on 3 different days.

Approximately 15 minutes before application of the blue liquids, the nasal mucosa was decongested using 2 sprays of xylometazoline hydrochloride to either nostril. For application of the nasal drops, participants were asked to recline their head as much as possible. After that, approximately 0.2 mL of the blue liquid was pipetted into the nostril. The nasal spray was applied by 3 sprays (approximately 0.2 mL), with the nasal aerosol device directed toward the olfactory cleft. When using the squirt system, participants again reclined their head; the tube was placed in the nasal cavity parallel to the nasal septum, also directed toward the olfactory cleft. Again, the applied volume was 0.2 mL. Application of the liquids was always performed by the same investigator (M.S.). Documentation of the distribution of the blue liquid in the nasal cavity was then immediately performed by means of nasal endoscopy. Photographs were taken from the anterior and middle parts of the nasal cavity and the olfactory cleft.

Based on these photographs, the intranasal distribution of the dye was rated by 2 independent observers (M.W. and T.H.). The 2 observers were blinded to the applicator system used. The presence or absence of blue stains was rated for the nasal floor, the lower turbinate, the anterior septum, the middle of the septum, the head of the middle turbinate, the insertion of the middle turbinate, and the olfactory cleft (**Figure 2**). A score of 0 indicates the absence of dye, and a score of 1 indicates the presence of dye. For further analysis, the sum of the ratings was computed separately for all investigated areas. Results were statistically analyzed using a software program (SPSS version 12; SPSS Inc, Chicago, Illinois).

RESULTS

Use of the different applicators always produced different patterns of staining, except in the anterior septum, which seemed to be reached equally well by all 3 forms of application (Friedman test: $P = .12$) (**Figure 2**). The anterior part of the nasal cavity, including the nasal floor, the lower turbinate, and the anterior septum, was reached by all forms of application, most extensively by the nasal spray and the nasal drops. The nasal drops predominantly reached the nasal floor.

In the middle portion of the nose, including the middle of the septum, the head of the middle turbinate, and the insertion of the middle turbinate, almost no dye was seen when drops were applied. In only 1 participant was the head of the middle turbinate stained. When the dye was applied as a spray, staining was present in the middle portion of the nose but in fewer participants compared with in the anterior part of the nasal cavity.

When looking at the olfactory cleft, the part of the nose that was most interesting to this research, nasal drops did

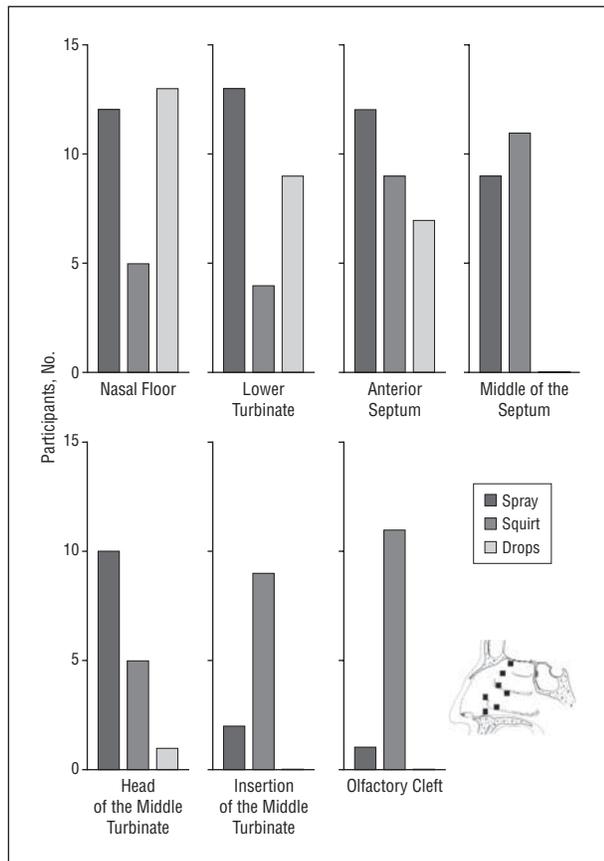


Figure 2. Results of the distribution of dyed liquid in the nasal cavity applied using 3 different applicators: nasal drops, nasal spray, and a squirt system. Nasal drops predominantly reached the nasal floor. The nasal spray was widely distributed in the nasal mucosa. Only with the squirt system was the olfactory cleft reached effectively. The inset is a schematic drawing of the investigated sites. Use of the different applicators always produced different patterns of staining, except in the anterior septum, which seemed to be reached equally well by all 3 forms of application (Friedman test: $P = .12$). $P = .002$ for the nasal floor and the lower turbinate, $P < .001$ for the middle of the septum, the insertion of the middle turbinate, and the olfactory cleft, and $P = .004$ for the head of the middle turbinate.

not seem to reach it in any of the 15 participants. When using the nasal spray, the olfactory cleft was reached in 1 participant only. Finally, when the squirt system was used, the olfactory cleft was reached in 11 of 15 participants (73%) (Figure 2 and **Figure 3**).

COMMENT

This study has 3 major findings. First, nasal drops predominantly reached the nasal floor, which confirms previous observations.¹⁷ Kubba et al¹⁷ also applied blue nasal drops in a reclined head position and found the blue dye along the nasal floor. When applied in such a form, the drops seem to obey the forces of gravity and the direction of mucociliary clearance¹⁸ and, thus, are transported from the anterior part of the nose to the nasopharynx. The nasal drop instillation was examined with the head reclined because other head positions (eg, bending the head over the edge of the bed or using the Mecca position) are not comfortable for patients and, thus, would reduce compliance significantly.^{19,20}

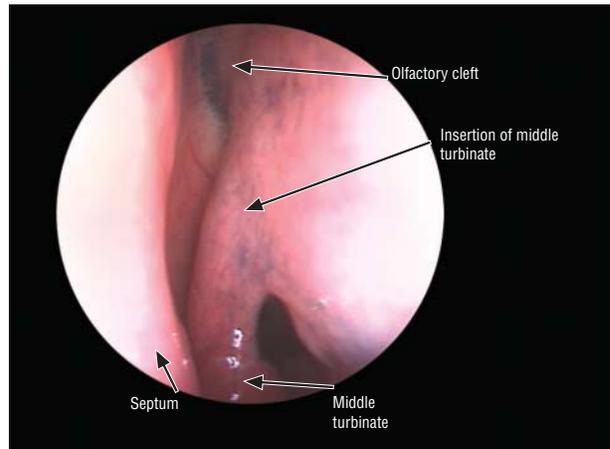


Figure 3. Example of the distribution of the dye in 1 nasal cavity using the squirt system. The blue dye can easily be seen in the olfactory cleft.

Second, the nasal spray was widely distributed in the nasal mucosa; however, it was intercepted by the middle turbinate and did not reach the olfactory cleft effectively. These results resemble those from previous research²¹ in which nasal sprays have been presented with different droplet sizes or different angles at which the spray was presented. Newman et al,²² in 10 healthy individuals, investigated the distribution and the clearance of aerosol from nasal pump spray using gamma camera scans; they found most of the spray only in the anterior part of the nose. Similar results were described by Weber et al²³ using endoscopic documentation of the distribution of a sodium fluorescein solution with a pump spray, where most of the substance was found at the anterior septum, and Bateman et al,²⁴ who compared 2 different spray techniques also using fluorescent solutions.

Finally, using the squirt system, the olfactory cleft was reached in most participants, which is a new and unique finding. These data partly explain why relatively few patients benefit from intranasal spraying of corticosteroids in the case of sinonasal olfactory loss because this is possibly founded in the fact that the drug does not reach the olfactory cleft when using traditional applicators. Using an appropriate technique for drug application might result in increasing the local corticosteroid dose in the olfactory cleft to maximize the therapeutic effect. Using a squirt system, higher efficiency of topical corticosteroids in the case of sinonasal hyposmia or anosmia could be expected, although the success of this therapy is subject to numerous other modulating factors.

Moreover, individual anatomical variation of the nasal cavity affects the distribution of intranasal drugs. For example, high septal deviations can be problematic in applying drugs to the olfactory cleft even when the squirt system is used. Furthermore, local administration of nasal drugs by the patients themselves allows little control of the effective amount of drug reaching the olfactory cleft. Extensive instruction regarding use of the applicator system, including practical training of the correct application technique together with the ears, nose, and throat specialist, would minimize incorrect handling of such a device; it certainly would help improve patient compliance. Both factors seem to be significant in terms of the

outcome of this therapy so that it is unforeseeable how such a system would work in practice.

In the present study, the participants' nasal mucosa was decongested before administration of the dyed liquid. More research is needed to determine whether such an additional maneuver is important for the clinical success of local therapy with corticosteroids. In clinical practice, however, this could be attempted relatively easily by instructing the patients to use a nasal douche with an isotonic solution of warm water to clean the nasal cavity and to decongest the nasal mucosa before application of the topical corticosteroid.

The present study should serve as a pilot study. It has a high priority because the results point out 1 possible reason why topical treatment of olfactory dysfunction does not work efficiently. To this day, the conservative treatment of olfactory disorders is disappointing. Numerous therapeutic trials have not been useful. Because many patients are affected by olfactory loss, the development of adequate therapies for olfactory loss is indispensable. Future studies will investigate the effect of topical corticosteroids in patients with sinonasal smell disorders using different forms of application.

In conclusion, the present data suggest that previous failure of therapy with topical application of corticosteroids in patients with sinonasal olfactory loss may, at least in part, be due to the fact that the substances did not reach the olfactory cleft when using traditional applicators. When using a squirt system, however, it seems more likely that larger amounts of the drugs reach the olfactory epithelium.

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Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Scheibe and Hummel. *Acquisition of data:* Scheibe, Bethge, and Hummel. *Analysis and interpretation of data:* Scheibe, Witt, and Hummel. *Drafting of the manuscript:* Scheibe and Hummel. *Critical revision of the manuscript for important intellectual content:* Scheibe, Bethge, Witt, and Hummel. *Statistical analysis:* Hummel. *Obtained funding:* Hummel. *Administrative, technical, and material support:* Scheibe, Bethge, and Hummel. *Study supervision:* Witt and Hummel.

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