ORIGINAL ARTICLE

Nasal Gel and Olfactory Cleft

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KEYWORDS
Intranasal preparations; Distribution; Olfactory cleft

Abstract
Objective: To evaluate whether a nasal gel, administered using a radial-hole inhaler, reaches the olfactory cleft, and if a different administration method influences distribution.

Material and method: Sixteen healthy volunteers underwent a nasal endoscopy at 1 and 7 min after the administration of an intranasal gel, with a different method in each fossa.

Results: No dye deposition was identified at the olfactory cleft, middle turbinate or middle meatus. In all cases the gel was identified at the nasal vestibule. On the right side, the second most frequent dye identification area was the inferior turbinate, with a rate of 87% at the first minute and 75% at 7 min. It was followed by the septum (75% and 62%) and the inferior meatus (6.2% and 12.5%). On the left side, the second most frequent stained area was the septum (18.7% and 13.5%), followed by the inferior meatus (6.5% and 65%). No inferior turbinate staining was found in the left side. There was a significant difference in the deposition rate at the septum (P<.01) and inferior turbinate (P<.001), when both administration methods were compared.

Conclusions: No nasal gel, administered using a radial-hole inhaler, was found at the olfactory cleft, middle turbinate or middle meatus. Gel distribution was located at the anterior and inferior portion of the nose, independent of the administration method used. Significantly different gel distribution rates were found at the septum and inferior turbinate when the 2 administration methods were compared.

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PALABRAS CLAVE
Preparaciones intranasales; Distribución; Hendidura olfatoria

Gel nasal y hendidura olfatoria

Resumen
Objetivo: Identificar si un gel administrado mediante un inhalador de cabeza radial puede alcanzar la hendidura olfatoria y si su distribución intranasal se modifica según el método de aplicación.

Material y método: Se estudiaron 16 voluntarios a los que se administró un gel teñido de modo diferente en cada fosa, realizándose una endoscopia tras 1 y 7 min.

Resultados: No se identificó gel a nivel de la hendidura olfatoria, cornete medio o meato medio independientemente del método de administración utilizado. En el vestíbulo se identificó...
Introduction

The functions of the nasal cavity are filtering, warming and humidifying inspired air in order to protect the airway. Particles which become trapped in the nasal mucus are transported through the action of the cilia in the nasal epithelium towards the nasopharynx and the digestive system. The anatomical design of the nasal fossa facilitates the contact of air with the nasal mucosa and conditions airflow through it. The use of specific intranasal medication for local processes is useful as long as it reaches key areas such as the ostiomeatal complex or the Eustachian tube. Therefore, knowledge of its distribution is important, both to assess its effects and to evaluate possible side effects on sensitive areas, such as the olfactory epithelium.

Intranasal administration of medication is often used in sinus conditions, a problem affecting approximately 1 000 000 people per year in Spain,1 and nearly 40 000 000 in the U.S.A.2 Its safety has been confirmed in multiple studies1,3 and its advantages over the oral route include rapid bioavailability in the bloodstream, preventing degradation in the gastrointestinal tract and prior passage through the liver. Its disadvantages include poor contact with the nasal mucosa and difficulty to reach specific areas, critical to its therapeutic effect.2-7 There are multiple types of administration systems5,8 and head positions for better distribution,5,9 so there have been numerous key recommendations based on literature reviews.2 However, studies have shown that, using the usual methods, the distribution of intranasally applied medication is localised mainly in the anterior portion of the nasal cavity.

Anosmia has been reported as a side effect of intranasal medication, secondary to zinc content. A possible cause would be the contact of medication with the epithelium of the olfactory region,10 but the possibility of distributing a nasal gel at the level of the olfactory area is highly implausible.5

The aim of this study is to assess whether a viscous gel, administered through a nasal inhaler with a radial head, can reach the olfactory cleft, and whether its nasal distribution varies depending on the delivery system employed.

Material and Method

Study Population

The study was conducted among healthy volunteers who had been previously informed of its conditions and characteristics. As a prerequisite, they had to sign a consent form which included the study characteristics, the material used and its possible side effects. We studied a total of 16 volunteers whose medical histories were assessed in order to rule out nasal condition or use of medication that could affect study results. They all underwent nasal endoscopy in order to confirm the absence of septal or septopyramidal deformity, as well as to assess the visibility of the olfactory area according to the following grades: 0, not visible; 1, partially visible; 2, visible after introducing the endoscope 2 cm; and 3, easily visible. The visualisation characteristics of the olfactory cleft are shown in Table 1.

The mean age of patients was 25±3 years (maximum: 28; minimum: 22), distributed equally between men and women. None of them had a previous history of nasal or systemic disease or of use of topical or systemic medication in the previous month. The inclusion criteria are summarised in Table 2.

Study Period

The study was conducted in January 2012.

Statistical Analysis

We conducted statistical analysis using Fisher’s test, with a confidence interval of 95% (α=0.05).
Method

After assessing the visibility of their olfactory cleft, patients were given indications for nasal gel application, following different instructions for each nostril. In the right nostril, they had to place the applicator vertically, introducing its upper end into the nostril and breathing deeply at the time of gel application. In the left nostril, they had to place the applicator in a horizontal position, directing the upper end towards the outer edge of the left eye and without breathing deeply at the time of gel application.

Nasal endoscopies were performed 1 min and 7 min after applying the gel, in order to detect presence of dye in the following anatomical structures:

- Nasal vestibule.
- Septum.
- Inferior turbinate.
- Middle turbinate.
- Inferior meatus.
- Middle meatus.
- Olfactory cleft.

Material

The radial head applicator used in this study was a medication spray which administered 140 µl per dose (Fig. 1), manufactured by Aptar Pharma SAP #10277363. The liquid gel was produced by Unicep Packaging (Sandpoint, Idaho). It had no active ingredient and instead contained methylene blue (used as a dye), benzalkonium chloride, glycerine, hydroxyethyl cellulose, purified water and sodium chloride. The final viscosity of the product was 5500 cps. Gel ingredients and their percentages are shown in Table 3.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percentage</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyethyl cellulose</td>
<td>1.2</td>
<td>Viscosity</td>
</tr>
<tr>
<td>Glycerine</td>
<td>1.0</td>
<td>Stability</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>0.9</td>
<td>Isotonic buffer</td>
</tr>
<tr>
<td>Benzalkonium chloride</td>
<td>0.02</td>
<td>Preservative</td>
</tr>
<tr>
<td>Methylene blue</td>
<td>0.01</td>
<td>Dye</td>
</tr>
<tr>
<td>Purified water</td>
<td>∼97</td>
<td>Vehicle</td>
</tr>
</tbody>
</table>

Table 3  Ingredients and their Percentages in the Gel.

Results

We did not find stained gel at the level of the olfactory cleft, middle meatus or middle turbinate in any of the volunteers tested, on either side, in the endoscopy conducted at 1 min or at 7 min.

In all cases we found stained gel at the level of the nasal vestibule, in both nostrils and during both endoscopies.

On the right side, the inferior turbinate was the second location in frequency, with a percentage of dye of 87% at 1 min and 75% at 7 min. It was followed in frequency by the septum, with 75% and 62% at 1 min and 7 min, respectively, and by the inferior meatus, with 6.2% and 12.5% at 1 min and 7 min, respectively.

The distribution of dye on the left side was more discreet. The second area in frequency was the nasal septum, with 18.7% and 13.5% at 1 min and 7 min, respectively, followed by the inferior meatus, which presented 6.5% in both endoscopies. Dye was not located in the inferior turbinate on this side.

The Fisher test showed significant differences in the distribution of gel at the level of the septum (P<.01) and inferior turbinate (P<.001), when comparing both methods of application (Table 4).

Discussion

The result of our study shows that a viscous gel administered through a nasal applicator with radial head was not able to reach the upper portion of the nasal fossa, as no dye was found in the olfactory cleft, middle turbinate and middle meatus. The modification of the application method did not result in better distribution at the top of the nasal fossa and only showed differences in distribution at the levels of the septum and inferior turbinate. Previous studies have shown that the distribution of medication administered intranasally is mainly located in the anterior nasal fossa (septum, vestibule and inferior turbinate) regardless of the application method employed.2,7,11 The nasal valve area is the narrowest part of the nasal fossa, separating the vestibule from the fossa itself. This structure is located about 2 cm from the edge of the nostril and has a
midsection of about 0.7 cm. The greatest resistance to airflow takes place at the inferior turbinate head level. All these anatomical characteristics justify the difficulties for the passage and distribution of gel to deeper and superior areas of the nasal fossa.

This study was performed on healthy individuals without previous nasal condition or nasal obstruction and with a visible olfactory area, so additional obstructive factors were ruled out. We did not use topical anaesthesia or pledgets soaked in vasoconstrictor so as not to alter the characteristics of the nasal mucosa, avoiding the appearance of rhinorrhea and sneezing which would introduce a bias in the distribution of gel.12

The stained gel was found in all cases in the nasal vestibule, an area lined with multilayered squamous epithelium, unable to transport and mobilise secretions. Therefore, the gel remained at that location until it disappeared or was eliminated by the patient.

Ciliated epithelium, located after the nasal valve, is capable of transporting nasal mucus and any substances trapped in it to the nasopharynx. The mean nasal mucus clearance time in healthy individuals is 30 min,13 although this period may vary depending on the anatomical characteristics of each individual, local disease, mucous characteristics and use of medication.13,14 No significant differences were found in nasal mucus clearance time when comparing a saline nasal spray and a gel spray, both stained with fluorescein.7

Due to its high viscosity, the nasal gel offered a lower tendency to drip, as well as reducing unpleasant taste sensations related to swallowing of the product.5 Since the direction of transport by ciliated epithelium is towards the nasopharynx and due to the effect of gravity, we can assume that transport of the gel towards the top of the nose after 7 min is very unlikely.

The modifications made on applicators and solutions have shown best results with sprays in which the pressure is obtained by manual pumping rather than pressurised sprays,15 but no improvement in distribution was obtained when comparing nasal sprays and drops.8,16,17 A previous study, which used a single-orifice applicator, showed similar results, with examinations performed up to 15 min after gel application,18 with no changes in explorations conducted in 45 patients. Therefore, we decided not to perform endoscopies after 7 min, since this procedure causes discomfort for patients and increases rhinorrhea, a factor that could affect the results of the study.

Modifications were designed to enable passage of the nasal valve and thus increase distribution in critical areas, mainly at the level of the nasal infundibulum, a key area in sinonasal conditions.8

Scheibe et al. studied different methods to reach the olfactory area. They considered that, since systemic corticosteroids were effective in the treatment of sudden anosmia, topical corticosteroids could also be useful, and concluded that the reason was due to their inability to reach the olfactory area.6 They reached the olfactory area in 73% of cases in which dyed saline solution was injected into the nostril using a syringe with a needle. This percentage dropped to 6.6% when the serum was applied with a spray and to 0% when it was administered as drops. A vasoconstrictor was used in all subjects 15 min before application of the serum and 3 consecutive doses were used.

The position of the head also affects intranasal distribution because airflow and gravity hinder the arrival of medication to the top of the nose, a critical area in sinonasal condition.2,8,9,19 Cannady et al. found that, in patients who had previously undergone endoscopic sinus surgery, with 3 drops of fluorescein-dyed dexamethasone applied to a patient in the nasal vestibule with the head vertex placed toward the ground (a position known as ‘‘praying to Mecca’’), the deposit at the olfactory area level was higher if the position was maintained for 5 min than if it was maintained for only 1 min.9 They found no differences between applying the product and maintaining the head vertex toward the ground for 1 min, and application of the product through a syringe inserted into the nostril between 3 and 5 mm and directed towards the external edge of the ipsilateral eye.9 Merkus et al. found no differences in distribution at the level of the middle meatus when comparing 4 different head positions (upright, hyperextended, on one side and with the vertex toward the ground) and 3 different applicator models.8 They concluded that the position with the vertex towards the ground enabled greater product distribution at the top of the nasal fossa, and that this could improve the delivery of medication to the olfactory area in patients with nasal polyposis.8

<table>
<thead>
<tr>
<th>Area</th>
<th>Right Side</th>
<th>Left Side</th>
<th>Value of P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Vestibule 1 min</td>
<td>16</td>
<td>100</td>
<td>16</td>
</tr>
<tr>
<td>Vestibule 7 min</td>
<td>16</td>
<td>100</td>
<td>16</td>
</tr>
<tr>
<td>Septum 1 min</td>
<td>12</td>
<td>75</td>
<td>3</td>
</tr>
<tr>
<td>Septum 7 min</td>
<td>10</td>
<td>62.5</td>
<td>2</td>
</tr>
<tr>
<td>Inferior turbinate 1 min</td>
<td>14</td>
<td>87.5</td>
<td>0</td>
</tr>
<tr>
<td>Inferior turbinate 7 min</td>
<td>12</td>
<td>75</td>
<td>0</td>
</tr>
<tr>
<td>Inferior meatus 1 min</td>
<td>1</td>
<td>6.2</td>
<td>1</td>
</tr>
<tr>
<td>Inferior meatus 7 min</td>
<td>2</td>
<td>12.5</td>
<td>1</td>
</tr>
</tbody>
</table>

No., number of cases with positive dye identification; NS, not significant. Values with significant differences are shown in bold (P<.05).
Taking a deep breath while administering the product was not associated with better distribution in the nasal fossa.\textsuperscript{2,19} We found a better distribution in the head of the inferior turbinate, but did not identify the presence of gel at the level of the middle turbinate, middle meatus and olfactory cleft.

Guo et al. analysed intranasal distribution in terms of different viscosities with the product applied and found no differences when combining different methods of application. They concluded that different methods of application do not alter distribution because airflow has little influence on product distribution and deposition.\textsuperscript{20} Particles leaving the applicator head impact on the vestibule and head of the inferior turbinate, without the ability to change direction and adapt to the airflow present in the area of the turbinate.\textsuperscript{17}

Multiple methods have been used for the study of intranasal distribution of medication (isotopes, dyes, endoscopy, collection of product on pledgets), each with different advantages and disadvantages.\textsuperscript{6} This variability makes comparisons between studies more difficult.

Intranasal endoscopic identification of dyes has been used in multiple studies.\textsuperscript{7,19,21} It is assumed that if the dye is identified at the level of the head of the middle turbinate, then it is possible to obtain distribution in that area, which is critical in sinonasal involvement.\textsuperscript{4} The sample size employed in most studies, as well as the methodology, was similar to that used in our study, with the difference that we specifically aimed to identify the dye at the level of the olfactory cleft, did not employ vasoconstrictor or anaesthesia, and the olfactory area was visible in all subjects.

Intersubject variability was minimised because even though subjects administered the product themselves, they were controlled directly by an observer, so as to ensure that they followed the correct procedure. There are no studies which analyse inter- and intrasubject variability, and which can provide information on the effect of incorrect product application due to not following instructions.

There have been reports of anosmia secondary to intranasal use of products containing zinc.\textsuperscript{10} Also, olfactory epithelium necrosis has been found in human nasal tissue cultures and in mice exposed to the product.\textsuperscript{22} Lim et al. mentioned the difficulty of depositing nasal gel in the olfactory area of a non-anaesthetised guinea pig as an argument to criticise the methodology of the study by Slotnick et al.\textsuperscript{22} In their study, Slotnick et al. found no relationship between a gel containing zinc and anosmia.\textsuperscript{23}

Regardless of the effect that zinc may cause on the olfactory epithelium, contact of zinc with the olfactory mucosa is necessary to generate damage in the olfactory epithelium. Therefore, the hypothesis is unlikely, taking into account that in our study we found no presence of dye in the olfactory area or in its vicinity. In clinical cases associated with the description of anosmia syndrome related to zinc, patients clearly reported burning sensation and olfactory impairment immediately or hours after administration of nasal gel while taking a deep breath. In our study, both with deep inspiration and without it, with the applicator in a vertical or horizontal position, gel distribution was localised in the anterior portion of the nose. This distribution did not change in the exploration conducted after 7 min.

Conclusions

Our study supports the concept that a viscous nasal gel is distributed in the anterior and inferior parts of the nasal fossa, primarily at the levels of the vestibule, septum and inferior turbinate, and that this distribution is not affected by the position of the applicator or by taking a deep breath at the time of application. We did not identify the presence of dyed gel in the middle turbinate, middle meatus and olfactory cleft, neither after 1 min nor after 7 min of product application. Moreover, this finding was not affected by different methods of product application. Therefore, we consider that the contact of a nasal gel with the olfactory epithelium of the olfactory cleft is highly unlikely.

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Conflict of interests

The authors have no conflict of interests to declare.

References