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A quantitative analysis of the intranasal delivery of topical nasal drugs to the middle meatus: spray versus drop administration

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Abstract

The delivery of nasal drugs specifically to the middle meatus is of critical importance in the medical treatment of rhinosinusitis. In this respect, topical nasal drug administration by drops has generally been perceived to be superior to nasal sprays, although there is a lack of evidence to support this notion. This study aims to compare the intranasal delivery of nasal sprays and drops to the middle meatus *in vivo*, using a novel quantitative method. A surgical patty was placed in the middle meatus. Radio-labelled topical nasal drops and aqueous sprays were administered in a standardized fashion in normal volunteers (10 nasal cavities). The subsequent absorption of administered radiolabelled saline on the patty was measured using a gamma counter. A randomized prospective crossover design was used for the study. The mean percentage (range) of absorbed administered saline on the swab was 8.7 (0.3–39.5) and 9.7 (0.03–20.4) for the spray and drop administration techniques respectively ($p = 0.8$). Thus, there is wide variation in the delivery of topical nasal drugs and the perceived superiority of nasal drop administration, in terms of delivery to the middle meatus, may be incorrect.

Key words: Nasal Cavity; Drug Administration, Intranasal

Introduction

Most topical nasal medication is administered as aqueous sprays. Previous studies in intranasal drug distribution using radiolabelled isotopes *in vivo* have demonstrated that most (50–80 per cent) of the deposition is at, or proximal to, the nasal valve, with relatively small quantities penetrating through to the ciliated areas of the nasal cavities.[1,2]

The issue of drug distribution to specific areas of the nasal cavity has received little attention. The middle meatus is the critical area of the nasal cavity in chronic sinusitis and nasal polyposis.[3,4] Most topical nasal medication is administered as aqueous sprays. Drugs for rhinosinusitis and nasal polyps are effective when delivered by aqueous spray,[5] suggesting that some of the delivered drug must reach the area of the middle meatus. However, it is known that the intranasal distribution of nasal sprays is sub-optimal, particularly with respect to the amount of delivered spray that penetrates the nasal valve.[1,2] Topical nasal drug administration by drops may be superior in this respect.[1,6] It is also assumed that nasal drops, administered in the correct fashion, may have a superior intranasal distribution, specifically in the region of the middle meatus. Betamethasone nasal drops have been shown to be effective in the treatment of nasal polyposis and chronic rhinosinusitis.[7,8] However, topical nasal betamethasone drops have significant systemic activity.[9] This raises the possibility that the good clinical results with nasal drops may be partly due to this. Hence the assumption that nasal drug distribution is superior with drops may be quite incorrect.

The aim of this pilot study was to compare the delivery of nasal sprays and drops to the middle meatus using a novel quantitative method of assessing intranasal distribution to this area.

Materials and methods

Subjects

The subjects were healthy volunteers, with both nasal cavities being studied in each subject. The exclusion criteria were: 1) chronic nasal disease, 2) significantly deviated septum (defined as the inability to pass a 4 mm nasendoscope), 3) current upper respiratory tract infection (within two weeks), 4) pregnancy and 5) occupational exposure to ionizing radiation. Approval was gained from the hospital ethics committee and an ARSAC certificate was obtained. All subjects gave their informed consent to enter the study.

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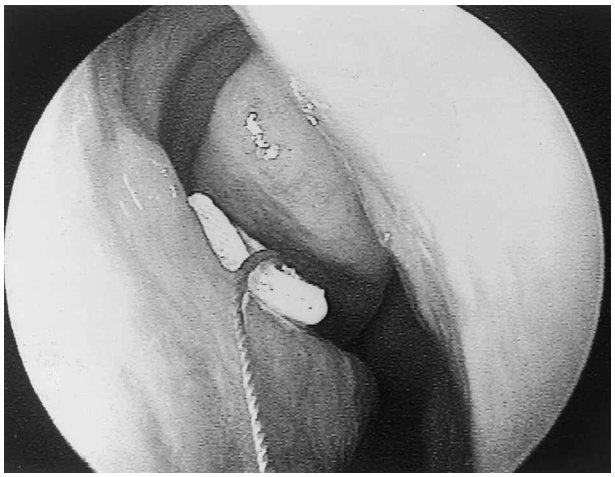

FIG. 1
Endoscopic photograph showing surgical patty in the entrance to middle meatus.

Protocol

Ten nasal cavities in five subjects were studied. A prospective randomized crossover study design was used. The subjects were randomized into two groups, to have nasal drops or spray first. Co-phenylcaine spray was administered to each nasal cavity. After five minutes, a surgical patty (7 × 7 mm, Johnson and Johnson) was lodged with the use of a 2.7 mm 0° nasendoscope between the uncinate process and the middle turbinate anteriorly at the entrance of the middle meatus. This was done in a standardized fashion, with the inferior end of the patty placed level with the inferior margin of the middle turbinate and the anterior end level with the anterior end of the middle turbinate (Figure 1). Radio-labelled drops/spray were immediately delivered in a standardized fashion and five minutes later the swab was withdrawn via a sheath (a modified insulin syringe) to avoid contamination with radioactivity delivered proximally. On a separate day the administration mode was swapped and the procedure repeated.

Preparation of Tc99m DTPA/saline mixture and method of drug delivery

50 MBq Tc99m-DTPA (Nycomed Amersham) in a volume of 1–2 ml was injected into a 100 ml bottle of saline. The mixture was then withdrawn and used to fill either droppers or spray bottles. Aliquots were withdrawn to use as standards in the gamma counting.

To administer the solution of drops, 0.2 ml was put into an empty Flixonase Nasule® (Allen and Hanbury). The subject adopted a head dangling position as described by Mygind.[10] The nasule was emptied vertically into the subject's nasal vestibule as far as it was possible. The subject remained in position for five minutes until the patty was removed. The spray was delivered from a standard aqueous spray. A Nasacort® (Rhone-Poulenc Rorer) spray was chosen because its top could be easily unscrewed. The spray delivered 0.1 ml per spray and two sprays (total of 0.2 ml) were administered to each nasal cavity in a saggital plane with a 45° angulation by one of the investigators.

The droppers and spray bottles were weighed immediately before and after administration to determine the administered radioactivity. The administered activity was 200 kBq per subject, giving an effective dose of approximately 6 μSv (comparable to one day of background radiation).

Measurement and statistical analysis

The primary outcome measure was the amount of radioactivity absorbed onto the patty, taking into account any residue on the inside of the sheath. This was expressed as a percentage of administered activity, calculated from the pre- and post-administered spray/dropper weights. After withdrawing the patty via the sheath, the external surface of the sheath was wiped clean. The amount of radioactivity delivered to the patty was the total of the activity of the patty itself and the activity of the sheath. This allowed any activity left on the inside of the sheath, when withdrawing the patty into it, to be taken into account. The standards, patties and sheaths were counted in a multivial gamme counter for 10 minutes. The Wilcoxon matched pairs test was used to compare the delivery by drops and by spray using the SPSS 9.0 software package. The order of administration was tested for as a potentially confounding variable.

Results

There was wide variation in the delivery of administered drug to the middle meatus. The range of uptake, expressed as a percentage of administered drug, ranged from 0.3 to 39.5 per cent for spray and from 0.03 to 20.4 per cent for drops (Figure 2). In some nasal cavities, one administration technique was superior and the opposite was true for others. Overall, there was no difference in the administration methods ($p = 0.8$) (Table I). There was also no period effect ($p = 0.33$).

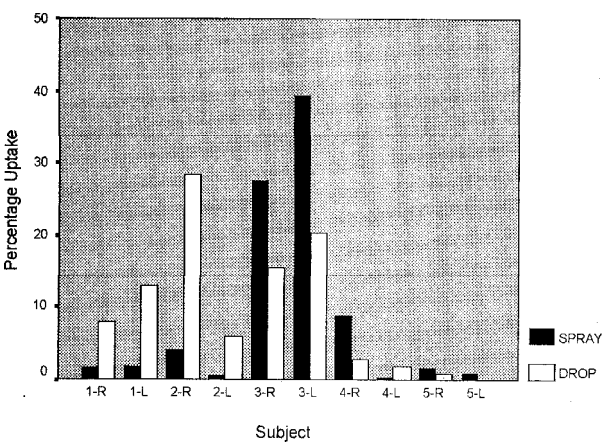

FIG. 2
Absorption of administered drug on the patty for each subject with each method of administration.

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TABLE I
COMPARISON OF DRUG DELIVERY TO THE MIDDLE MEATUS BY SPRAY AND BY DROP

	Percentage uptake of administered drug	
Mode of delivery	Mean	SD
Spray	8.7	13.6
Drop	9.7	9.5

$p = 0.8$

Discussion

The results of this study did not demonstrate a difference between drop and spray administration of topical nasal drugs, in terms of delivery to the region of the middle meatus. However, we also found that the variability of delivery of radioactivity to the middle meatus was marked. This aspect of nasal drug delivery has not been addressed hitherto. The inter-subject variation is marked for both modes of administration. It also seems that in some nasal cavities, one administration method is superior to the other. Thus, this study rather than demonstrating either the superiority or equivalence of the administration methods in a given individual, shows that the optimal method varies. The clinical relevance of this is that in patients who do not respond to intranasal steroids by one route, it is worth trying a different mode of administration before regarding rhino-sinusitis as 'steroid resistant'. This study has not been designed to show intra-subject variation. It is likely that this variation may be significant. The problem with measuring this variation is that it is impossible to determine how much variation is due to true variation in drug distribution in the nasal cavity and how much may be due to measurement variation and errors. If this methodology is to be further assessed, this should be the next step.

Delivery of drugs to the middle meatus by drops was demonstrated, which infers that betamethasone drops work, in part at least, by local action. This is further supported by the fact that a newly available nasal steroid drop with minimal systemic effect is effective in the treatment of nasal polyposis.[11]

Research into topical nasal drug distribution has generally been neglected in rhinology. Most work has been carried out using radiolabelled drugs and saggital scintigraphic scans for assessment.[1,12] The problem with the previous isotope studies is that they fail to show the drug distribution (a) in detail and (b) with regard to the individuals' three dimensional intranasal anatomy. These studies can give an impression of intranasal distribution that is confined to qualitative descriptions. The proportion of spray that reaches the ciliated epithelium is more readily assessed by observing the proportion of spray transported by mucociliary flow but useful quantitative information over and above this is not forthcoming. A more recent technique aims to use positron emission tomography (PET) to measure radioactivity of administered isotopes in relation to three dimensional areas of the nose and sinuses.[13] However, the study fails to show that the technique has the precision and resolution required to measure the intranasal delivery to very specific areas. Other described methods of intranasal drug distribution assessment include *in vitro* methods using nasal casts made from human cadavers.[14] The problems here are: (a) that it is difficult to incorporate the nature of the vestibule into a cast and (b) the cast material and lining is completely different from nasal mucosa. Furthermore, the outcome measures in studies using casts have tended to be rather loose qualitative descriptions of nasal drug distribution, which is also a criticism of studies that simply describe the endoscopic appearances of the nasal cavity after the instillation of dyed solutions.[15]

There are two reasons why the results of this study may not extrapolate to patients with rhino-sinusitis. Firstly, we used normal subjects rather than patients with rhinosinusitis. Secondly, the subjects had a decongestant administered beforehand. The significance of this is that it may be possible that any superiority of nasal drug delivery to the middle meatus by drops is only manifest in patients with nasal mucosal congestion (and therefore poor access to the middle meatus). Certainly, the results of this study are not expected to be generalizable to patients with gross polyposis. The use of decongestant was necessary not only to minimize any confounding effect of the nasal cycle but also to enable correct and easy positioning of the patty in the middle meatus. Therefore, this potential pitfall of the technique is unavoidable. However, no alternative methods of quantifying delivery of drugs to specific areas in the nose, have been described and evaluated. One of the authors (JJH) has described a photographic technique of estimating distribution to the middle meatus using endoscopic photography of the middle turbinate.[16] However, the central assumption of this technique is that the drug is delivered to a reasonably wide area for the middle turbinate to act as a guide to distribution to the neighbouring middle meatus. This is applicable to a spray but not to drops because drops could penetrate the middle meatus without necessarily coating the anterior end of the middle turbinate.

Another problem in interpreting the clinical relevance of this study lies in the rigid standardization of administration techniques involved. Patients who actually use topical nasal drugs may not comply with the proper administration techniques. This is likely to be particularly relevant to the instillation of nasal drops, where it can be assumed with some justification that a significant proportion of patients do not use the recommended techniques. Therefore, any results pertaining to nasal drops in particular represent the optimal intranasal drug distribution, which may be quite different from that achieved clinically in patients.

In conclusion, we have described a novel quantitative technique for measuring nasal drug distribution to the middle meatus *in vivo* that is applicable to both spray and drop medication. One disadvantage is the necessity to decongest the nose to perform the technique. We did not demonstrate any superiority of nasal drops in terms of distribution

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to the middle meatus compared to nasal sprays in normal subjects overall. However, there is considerable inter-individual variation in terms of superiority of administration technique. The clinical relevance of this is that patients who do not respond to topical steroids administered by one delivery method (drops or spray) should be given treatment by the alternative method for before being considered as steroid resistant.

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