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The 'best method' of topical nasal drug delivery: comparison of seven techniques*

P. Merkus[1], F. A. Ebbens[2], B. Muller[2], W. J. Fokkens[2]

[1] Department of Otorhinolaryngology & Head and Neck Surgery, VU Medical Center, Amsterdam, Netherlands
[2] Department of Otorhinolaryngology & Head and Neck Surgery, Academic Medical Center, Amsterdam, Netherlands.

SUMMARY

Objective: *To determine whether there is a 'best' technique for delivering drugs to the middle meatus.*
Design: *Single-blind cross-over study in healthy individuals using endoscopic video-imaging.*
Participants: *A dyed test formulation was administered intranasally on seven non-sequential days to ten healthy individuals with no 'nasal' history. The participants were recruited through advertisement.*
Main outcome measures: *Comparison of seven different techniques, 20 nostrils and 140 endoscopic videos for the deposition patterns of dyed test formulation. Analysis was possible in 90% of all endoscopic videos. Three head positions were tested for both nasal drops and nasal sprays.*
Results: *Deposition of dyed test formulation near the middle meatus was observed in 43% of all observations. No significant differences were observed in terms of delivery between any of the seven techniques.*
Conclusions: *Our study suggests there may not be a single 'best' technique for topical nasal drug delivery. A more individual approach to topical nasal drug treatment, taking anatomy and head position into account would seem to be more appropriate.*

Key words: nasal drug delivery, nasal spray, nasal drops, distribution, nasal polyposis

INTRODUCTION

Based on a review of the literature, the American Academy of Otolaryngology-Head and Neck Surgery Foundation has tried to define the best technique of administering intranasal corticosteroids [1]. Unfortunately, they failed to provide us with definitive conclusions. This is remarkable, since large groups of patients receive daily corticosteroids for the treatment of nasal polyposis, allergic rhinitis, rhinosinusitis or chronic rhinosinusitis.

Reaching the middle meatus is of importance when treating both nasal polyposis and chronic rhinosinusitis [2], but individual anatomical and physiological differences challenge nasal drug delivery to this area. Furthermore, the great variety of used methods and small size of most investigational groups prevents consensus about the best technique for administering topical nasal drugs [1,3].

In this study we compared four nasal drug delivery techniques currently in use and tried to define the best technique for administering intranasal corticosteroids. In addition to the four techniques already in use, we investigated three new techniques for topical nasal drug delivery. These new techniques used the single-unit dose nasal spray, a known intranasal drug delivery device, re-designed to overcome the role of gravity and combining the advantage of a spray mechanism with the possibility of delivering drugs in non-upright head positions.

MATERIAL AND METHODS

Healthy volunteers

Healthy volunteers were recruited through an advertisement. Volunteers with frequent epistaxis, a history of smoking, an absent middle turbinate or a severe septal deviation (defined as severe enough to prevent visualisation of the anterior end of the middle turbinate without decongestion) were excluded. Volunteers taking medications (corticosteroids, antibiotics) known to interfere with nasal mucosa and volunteers having difficulties in assuming the different head positions for administration were excluded. All included subjects were required to read and sign an informed consent form. The study was approved by the Medical Ethical Committee of the Amsterdam University Medical Center.

Test drug formulation for spray and drop

The same dyed formulation was used in each test. The content of fluticasone nasal drops (Flixonase nasules® (1 mg/ml),

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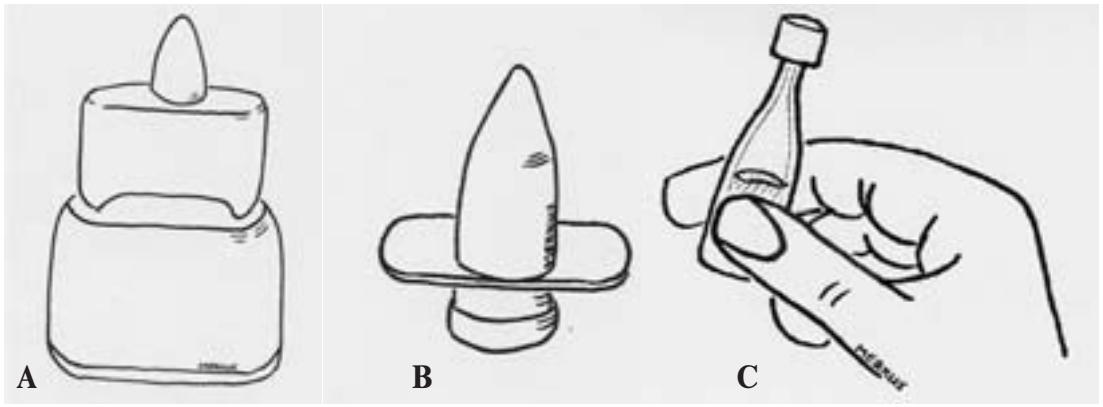

Figure 1a-c. Three drawings showing the devices used. a.. Container spray, a multidose spray, used in one head position; b. Unit–dose spray, an 'one time use' spray functional in different head positions; c. Nasule, an 'one time use' plastic container, used in different head positions.

	Sprays				**Drops**		
Device	Container Spray	Unit-dose Spray			Nasal Drops		
	HUR	LHB	LHL	HDF	LHB	LHL	HDF
Head	Head	Lying	Lateral	Head	Lying	Lateral	Head
Position	UpRight	Head	Head	Down	Head	Head	Down
		Back	Low	Forward	Back	Low	Forward

Figure 2 . Summary of the seven techniques used. The head positions are shown in Figure 2.

GlaxoSmithKline, Zeist, Netherlands) was used as the test formulation and dyed with 0.1% methylene blue (methylthionin chloride 1 mg/ml of pharmaceutical grade). In order to guarantee comparable volumes of test formulation in all test situations, the usual daily dose of fluticasone in a metered atomizing nasal spray (Flixonase®, GlaxoSmithKline), 2 puffs each nostril, (approximately 0.18ml) was used as the standard test volume. Dose and volume were checked by two physicians prior to delivery.

Nasal sprays

Metered atomizing nasal sprays for fluticasone (further referred to as 'container spray', Figure 1a) were emptied and filled with dyed test formulation. These devices deliver 0,089 ml during each spray. After priming, two puffs per nostril were administered (equals approximately 0.18 ml per nostril) to each volunteer sitting in the Head in Upright position (HUR).

The second spray, the unit-dose spray (Figure 1b, Bidose MK3®, Valois, France), was adapted by the manufacturer to deliver 0.18 ml of test formulation per nostril in one spray when filled with 0.20 ml (0.18 ml dose volume, 0.023 ml residual volume). The manufacturer supplied residual volumes and these were checked using pre- and post delivery weight measurements. The single-unit dose spray is, unlike the container spray mentioned above, capable of delivering drugs in different head positions against gravity. Three different head positions were tested (see head positions and Figure 2 and 3).

Nasal drops

Nasal drops were administered using nasules (Figure 1c, Flixonase nasules®). Each nasule was filled with test formulation to a total volume of 0.20 ml, delivering 0.18 ml after one firm squeeze (0.18 ml dose volume, 0.02 ml residual volume). Three different head positions were tested (see head positions and Figure 2 and 3).

Study design

Single-blind randomized crossover study using seven different nasal drug delivery techniques (Figure 2). Each volunteer was tested on seven non-sequential days.

Head positions

Head upright (HUR): This position is widely used for all multidose container sprays. All other head positions are explained below and drawn in Figure 3.

Lying head-back position (LHB): Lying down in supine position with the head just off the bed in hyperextension, so that the chin is the highest point of the head. This head position was first described by Proetz in 1926 [4,5] and modified by Mygind in 1979 [6].

Lateral head-low position (LHL) [7-9]: Lying on the side with the parietal eminence resting on the bed (no pillow or a pillow under the shoulders). The nasal formulation is administered to the lower nostril.

Head down and forward (HDF), also known as 'Praying to

3a. Lying Head Back (LHB)

3b. Lateral Head Low (LHL)

3c. Head-Down and Forward (HDF)

Figure 3a-c. Three head positions: a. Lying Head Back (LHB, chin as highest point), b. Lateral Head Low (LHL, lying on one side) and c. Head Down and Forward (HDF, 'Praying to Mecca').

Mecca' [12]: Kneeling down, placing the top of the head on the ground and the forehead close to the knees with the nostrils facing upwards.

Protocol

All healthy volunteers received instructions during the first visit. Subsequently, and on all other visits, the first ENT physician administered the test formulation using one of the techniques described in the study design (Figure 2). The delivery of dyed test formulation was directed towards the lateral epicanthus of the ipsilateral eye. Volunteers were not allowed to deliver the test formulation themselves. After administration, each volunteer had to remain in the position in which drugs were delivered for 60 seconds. The first ENT physician provided strict supervision of administration. Nose blowing was allowed prior to administration. During the test, vigorous sniffing and nose blowing were *not* allowed. In an adjacent room, a second ENT physician, who was not informed about the technique used, performed nasal endoscopy within three minutes after the administration of dyed test formulation. The drug delivery technique was revealed just before statistical analysis of the data.

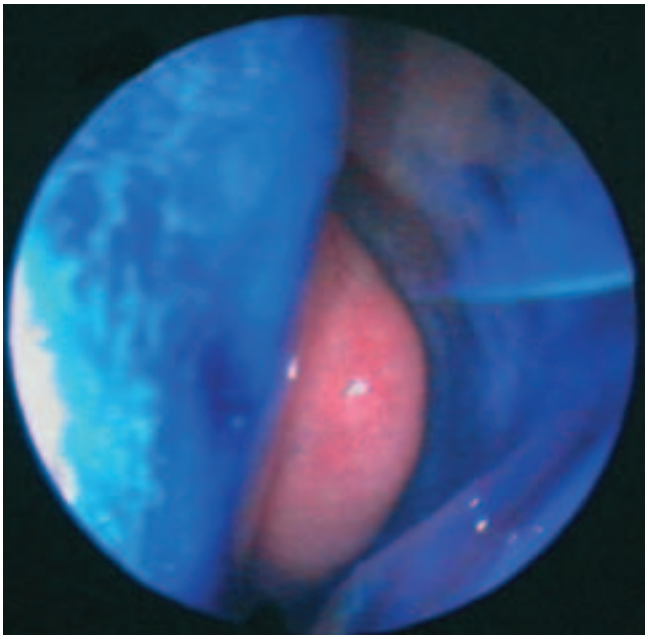

Figure 4. Photograph of an endoscopic view immediately after the administration of the test formulation. Dyed formulation is clearly visible lateral and medial (septum) of the middle turbinate.

Endoscopic investigation

A 2.7mm 0° Storz rigid nasendoscope was used and the images were recorded using digital video registration (Stroboview® 2000, Alphatron medical & microwave systems BV, Rotterdam, The Netherlands). The endoscope was placed near the anterior end of the middle turbinate and then retracted slowly while recording images. An example of endoscopic photo imaging is shown in Figure 4. This procedure is based on a combination of the photographic analysis described by Weber et al. [11,12] and the endoscopic evaluation described by Homer et al [13]. No local anesthetic or decongestant was used.

Video analysis

Three independent ENT specialists analyzed all video images. The deposition of dyed test formulation was scored as either 'head of the middle turbinate not visible' (not on the video/poor view), 'absence of dye' or 'presence of dye'. Dye scoring was rehearsed to reduce inter-observer variability. The analysis was based on observer consensus, with at least two observers independently agreeing on deposition scoring. This is a statistical valid method often used in histological grading [14]. The videos in which the middle turbinate was not visible were excluded from the analysis results.

Table 1. Dye around the head of the middle turbinate per technique.
Absolute figures for the seven techniques tested in twenty nostrils. 'Container spray' is a multi-dose spray and 'unit-dose spray' is a single-unit dose spray, used in different head positions (LHB = lying head back, LHL = lying head lateral and HDF = head down and forward). Overall, dye was present or absent in almost equal numbers of observations. In 90% of all endoscopies, clear observation of the middle turbinate was possible. The data are presented as percentages in Figure 5.

Absolute figures	Container spray	Nasal Drops LHB	Nasal Drops LHL	Nasal Drops HDF	Unit-dose Spray LHB	Unit-dose Spray LHL	Unit-dose Spray HDF	Total
Dye: absent	8	11	11	13	8	5	10	66
present	10	7	7	5	10	14	7	60
Head of the middle turbinate not visible	2	2	2	2	2	1	3	14
n	20	20	20	20	20	20	20	140

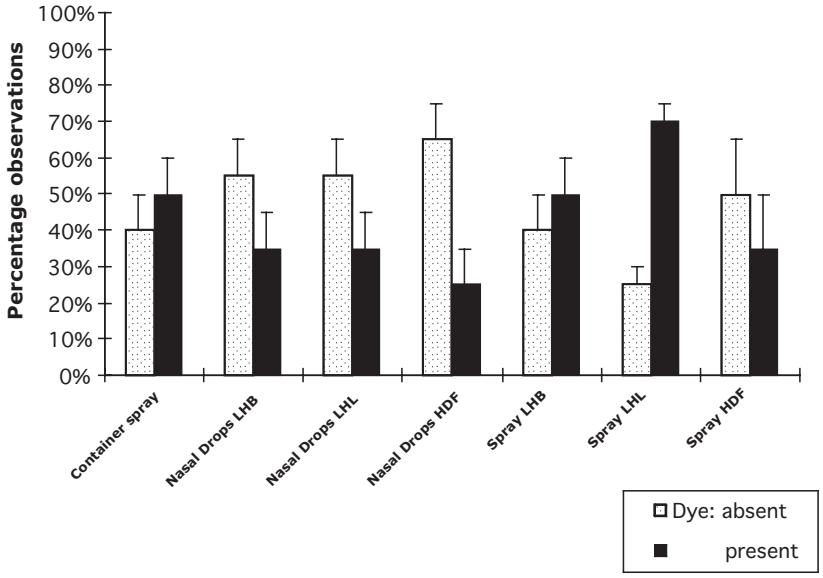

Figure 5. Presence or absence of dye around the head of the middle turbinate after nasal drug delivery using seven different techniques. The black bars (presence of dye) or white dotted bars (absence of dye) represent the percentages of observations with or without dye around the middle turbinate.

Statistical analysis

Statistical analysis was conducted with SPSS (version 12.01, SPSS Inc., Chicago, USA). Cochran Q non-parametric tests for related samples were performed to check for significant between-group variability. McNemar non-parametric tests for related samples were performed for between-group comparisons. P-values of less than 0.05 were considered statistically significant.

RESULTS

Ten volunteers were included, 2 males and 8 females with a median age of 23 (19- 28) years. Nostrils were evaluated separately (n=20). Seven different drug delivery techniques were compared and a total of 140 recorded endoscopies were analyzed.

Table 1 and Figure 5 show the overall presence of dye around the middle turbinate. Values scored as 'head of the middle turbinate not visible' were excluded from the analysis results (ten per cent of all observations). In general there was less dye towards the middle meatus (47% presence, 43% absence, Table 1).

Statistical analysis revealed no significant difference between the amounts of drug delivered near the head of the middle turbinate by the seven investigated techniques (Figure 5, $n = 7$, $p = 0.115$). Although not significant, a clear improvement in deposition near the head of the middle turbinate using the single-unit dose nasal spray was observed for all techniques (HUR, LHB and LHL head position, Figure 5). The single unit-dose nasal spray was superior to nasal drops in all head positions used. This difference attained significance when all observations for both delivery devices were taken together (Figure 6, n=3, $p = 0.039$). Caution should be taken when transposing these figures to the clinical setting (see discussion).

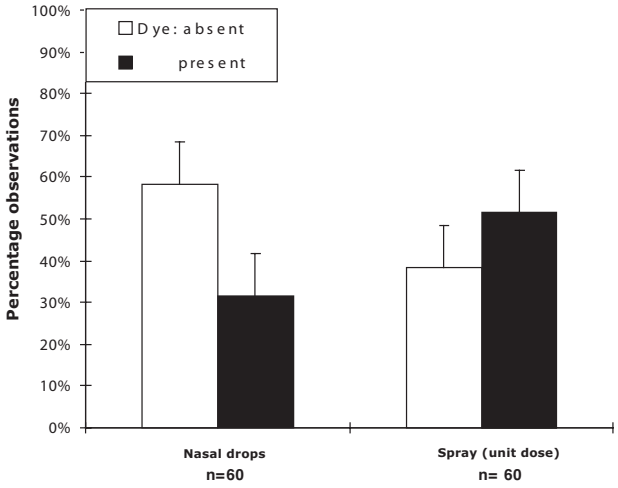

Figure 6. Comparison of nasal drops and the single-unit dose spray without regard to head position. The black bars (presence of dye) or white dotted bars (absence of dye) represent the percentage observations with or without dye around the head of the middle turbinate ($p = 0.039$, $n = 60$). Caution should be taken to convert these figures to the clinical setting.

In general, the different techniques for topical nasal drug administration were easily accepted, although most volunteers mentioned some discomfort during the HDF head position, confirming the findings of Kayarkar [15]. The test formulation was tolerated well, but some volunteers noticed some discomfort (sneezing, itching). No adverse effects were observed. In some cases, congestion disturbed the quality of endoscopic video imaging. These images were excluded from the analysis results.

DISCUSSION

Nasal drug delivery is a multifactorial process and therefore hard to investigate. Individual anatomical differences, different head position, the type of drug formulation, drug volume and different delivery devices all affect topical nasal drug delivery. Furthermore, since there are numerous investigational methods, comparison between studies is even more difficult [3]. All of these factors may explain why Benninger et al. in their thorough review, failed to arrive at definitive conclusions about the best technique for administering topical nasal drugs [1]. In our present study we tried to optimize the investigational method used for the assessment of topical nasal drug delivery by combining photographic analysis [11,12] with endoscopic evaluation [13] and by standardizing the test formulation, test volume and head position. Our standard volume throughout the experiments was chosen carefully on the basis of the daily volume of a nasal container spray (delivers around 0.18 ml after 2 puffs in one nostril) and was comparable to the volume delivered as nasule drops (half the content of one nasule, approximately 0.2 ml).

Despite the optimization of the study method, no significant differences were found between the seven topical nasal drug delivery techniques. On the basis of these and other results, it may be realistic to conclude that there is no such thing as 'a best technique' for topical nasal drug delivery. In a number of healthy volunteers, anatomical variations, although small, seemed to influence topical nasal drug delivery. This may explain the unsuccessful search for the best nasal drug delivery technique for a whole group, in spite of the best technique per individual. This has already been suggested by earlier publications [16].

We observed a trend indicating that the single-unit dose nasal spray was on the whole superior to nasal drops in a comparison of three devices (Figure 6). We believe this spray could be a promising new device for topical nasal drug delivery, but additional testing will be required to establish the true value of this innovative device. The longer tip of this nasal spray (bypassing the nasal valve area and vestibule hairs), the higher velocity of administration (to increase penetration) and the possibility of directing drugs may account for these differences. Again, we believe that further studies are necessary to confirm these results.

Our study reveals that all head positions commonly used for the delivery of drugs in nasal drops are equally effective, although a slight trend in favour of the LHB and LHL head position was observed, confirming the findings of Karagama et al. [17]. A similar trend was seen in drops and spray, which may indicate that head position, like anatomy and delivery device, is an independent factor determining the outcome of topical nasal drug treatment. Drug delivery to the nose via the HDF head position revealed that drugs are delivered at more cranial locations (data not shown). This head position may, therefore, be useful in the treatment of nasal polyps located superior to the middle meatus or in reaching the olfactory region.

Although our study provides important additional information about topical nasal drug treatment, we were unable to investigate some other important determinants of nasal drug delivery such as the variability between repeated drug administrations, the effect of time on nasal drug delivery (mucociliary transport) and quantification of the amount of dye reaching the middle meatus. Although an investigational method to quantify topical nasal drug delivery has been described by Aggarwal et al. [3], we think that this method will not identify a true 'best drug delivery technique' since local anesthetics and decongestants alter nasal anatomy and physiology significantly.

In general, we wish to stress that results form studies in healthy individuals are difficult to extrapolate to pathological conditions, such as major septal deviations, allergic rhinitis, chronic rhinosinusitis and nasal polyposis, and that additional studies in diseased patients will be necessary before implementing results in clinical practice.

From our study, we conclude that topical nasal drug delivery is multifactorial and hard to investigate, and that the identification of a single 'best technique' for topical nasal drug administration is unrealistic. A more individual approach to topical nasal drug

treatment, taking anatomy and head position into account seems more appropriate. We hope that future research will include the single–unit spray and patients instead of healthy volunteers.

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Paul Merkus
Department of Otorhinolaryngology & Head and Neck surgery
Vrije Universiteit Medical Center (VUmc)
KNO 1d-116
PO Box 7057
1007 MB Amsterdam
the Netherlands

Tel: +31 20 444 3690
Fax: +31 20 444 3688
E-mail: P.Merkus@VUmc.nl