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## Influence of anatomy and head position on intranasal drug deposition

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**Abstract** The objective of this study was to determine the influence of individual anatomical differences on intranasal drug deposition. The data of a comparison of seven different administration techniques in ten healthy volunteers was used in this single-blind crossover pilot study. After intranasal administration of a dyed test formulation, endoscopic video imaging was done on seven non-sequential days. The deposition pattern per individual around the head of the middle turbinate was analyzed for each technique and correlated with the individual anatomy. Decreased deposition of dyed test formulation in the target area around the head of the middle turbinate was observed in the presence of minor septal deviations, narrow nasal valve areas, or inferior turbinate hypertrophy; a lateral head position helps to bypass a minor septal deviation. Although results are preliminary, we conclude that anatomy and head position are important factors in the deposition of topical nasal drugs and may be the key to improving individual local nasal (steroid) treatment.

**Keywords** Nasal drug delivery · Nasal polyposis · Rhinosinusitis · Anatomy · Distribution · Head position

### Introduction

A recent thorough review shows that only eight studies have proven the efficacy of topical intranasal cortico-

steroids in the treatment of patients with chronic rhinosinusitis (five studies) and nasal polyposis (three studies) [6]. Although this treatment is often successful, topical corticosteroids sometimes fail to reduce polyp size effectively or to decrease rhinosinusitis complaints. Many factors determine the outcome of topical nasal drug treatment: formulation characteristics, delivery device, delivery technique, site of deposition, anatomy, pathophysiology, and compliance, for example. This means that there are many uncertainties confronting the ENT surgeon when optimizing treatment for individual patients.

It seems rational to aim for the middle meatus when treating nasal polyposis and chronic rhinosinusitis [22]. Several studies have looked at the best way to reach this area but, remarkably, the American Academy of Otolaryngology–Head and Neck Surgery Foundation has failed, on the basis of a review of these studies, to draw definitive conclusions regarding the best technique for topical nasal treatment [3]. An explanation could be the underestimation of the influence of individual anatomy. If anatomical obstructions reduce the delivery to the middle meatus of topical nasal drugs, it would seem unlikely that there is a single administration technique appropriate for all patients. In a recent publication [14], we confirmed the absence of a “best technique” for topical nasal drug delivery; in the present pilot study, we correlate the drug deposition data with the individual anatomical differences. Ten volunteers and seven techniques of drug delivery were used to determine whether anatomical obstructions influence drug deposition and whether obstructions can be avoided by changing the technique of administration.

### Materials and methods

#### Healthy volunteers

Healthy volunteers without nasal symptoms were recruited through an advertisement. Volunteers with

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frequent epistaxis, a history of smoking, an absent middle turbinate, a history of sino-nasal operations, or a severe septal deviation (defined as severe enough to prevent visualization of the anterior end of the middle turbinate without decongestion) were excluded. All anatomical differences were carefully described and recorded prior to inclusion. Patients with various anatomical differences (except for extreme septal deviations as described above) were included. Volunteers taking medication (prednisone, antibiotics) known to interfere with nasal mucosa and volunteers with difficulties in assuming the different head positions for administration were excluded. All subjects were required to read and sign an informed consent form. The Medical Ethical Committee of the Amsterdam University Medical Center approved this study.

#### Test drug formulation for sprays and drops

The same dyed formulation was used in each test. The test formulation selected was fluticasone nasal drops [Flixonase nasules<sup>®</sup> (1 mg/ml), GlaxoSmithKline, Zeist, Netherlands]. It was dyed with 0.1% methylene blue (methylthionin chloride 1 mg/ml of pharmaceutical grade). In order to ensure a comparable volume of test formulation in all test situations, the usual daily dose for fluticasone in a metered atomizing nasal spray (Flixonase, GlaxoSmithKline, Zeist, Netherlands, two puffs each nostril, approximately 0.18 ml) was used as the standard test volume.

#### Nasal sprays

Metered atomizing nasal spray for fluticasone (further referred to as “container spray”) was emptied and filled with dyed test formulation. This device delivers 0.089 ml during each spray. After priming, two puffs per nostril were administered (equals approximately 0.18 ml per nostril) to each volunteer seated with the head in upright position (HUR).

The manufacturer adapted a single-unit dose spray (Bidose MK3<sup>®</sup>, Valois, France) to deliver 0.18 ml of test formulation per nostril (fill volume 0.203 ml). This single-unit dose spray is, unlike the container spray, capable of delivering drugs in different head positions. Three different head positions were tested (see below and Table 1).

#### Nasal drops

Nasal drops were administered using nasules (Flixonase nasules). Each nasule was filled with 0.20 ml dyed test formulation in order to deliver 0.18 ml after one firm squeeze (0.18 ml dose volume, 0.02 ml residual volume). This resembles the prescribed dosage of “half a nasule” and is similar to the daily dose of the container spray. Three different head positions were tested (see below and Table 1).

#### Study design

A blind randomized crossover study using seven different nasal drug-delivery techniques (Table 1) was conducted. Each volunteer was tested on seven non-sequential days. The correlation between dye deposition and individual anatomy was analyzed.

#### Head positions

*Head upright (HUR)* This position is widely used for all multidose container sprays. The three other head positions are explained below and shown in Fig. 1.

*Lying head back (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 described first by Proetz [19, 20] in 1926 and modified by Mygind [16] in 1979.

*Lateral head low (LHL)* [17, 18, 21] 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 in the lower nostril.

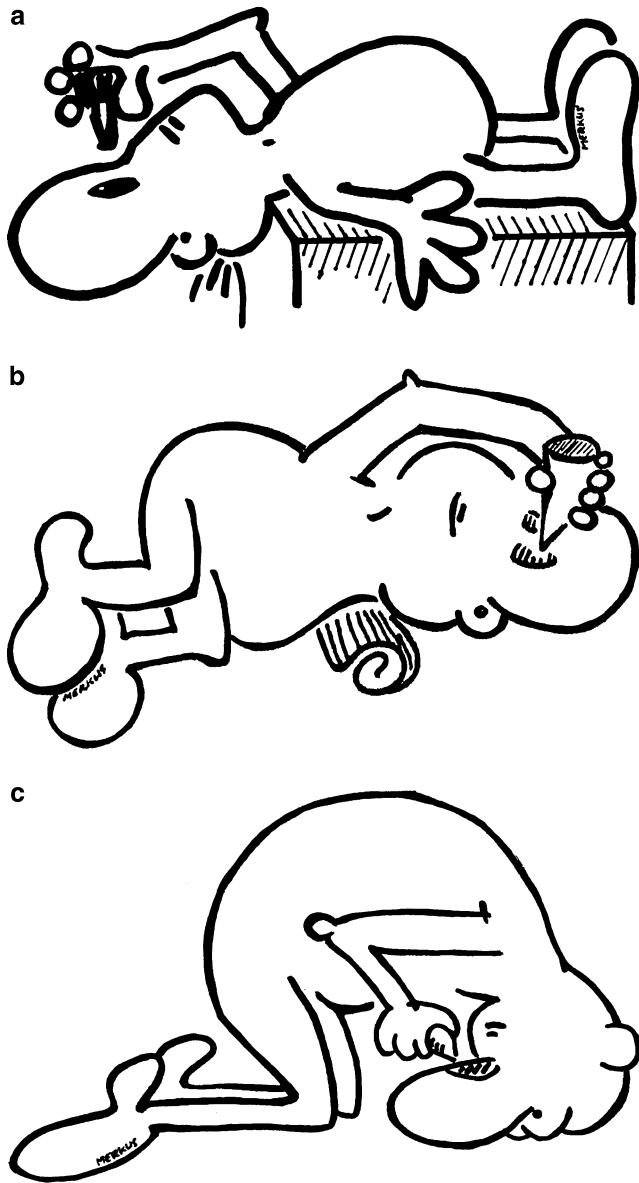
*Head down and forward (HDF), (Praying to Mecca)* [4, 13] Kneeling down with the top of the head on the ground and the forehead close to the knees with the nostrils facing upward.

#### Protocol

Three ENT physicians reviewed and graded the anatomical differences between the selected individuals. All healthy volunteers received instructions during the first visit. Subsequently, and at all later visits, an ENT

**Table 1** Summary of the seven techniques used. Figure 1 shows the head positions

Device	Sprays			Drops			
	Multi-dose container HUR	Single-unit dose		Nasules			
		LHB	LHL	HDF	LHB	LHL	HDF
Head position	Head upright	Lying head back	Lateral head low	Head down forward	Lying head back	Lateral head low	Head down forward



**Fig. 1** 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”)

physician administered the test formulation using one of the techniques described in the study design (Table 1 and Fig. 1). After administration, the volunteer remained in the same position for 60 s. Vigorous sniffing and nose blowing were not allowed during the test (this was only allowed prior to administration and after endoscopy). In the next room, a second ENT physician, who was not informed of the technique used for drug administration, performed a nasal endoscopy within three minutes after administration. The technique used for drug delivery was revealed after scoring of three independent observers and after closing of the database.

## Endoscopic investigation

A 2.7 mm, 0° Storz rigid nasendoscope was used and images were captured using digital video registration (Stroboview® 2000, Alphatron medical & microwave systems BV, Rotterdam, Netherlands). The endoscope was placed near the anterior end of the middle turbinate and subsequently retracted slowly while recording the images. This procedure was based on a combination of the photo analysis described by Weber and Keerl [25] and the endoscopic evaluation described by Homer and Raine [9]. No local anesthetic or decongestant was used.

## Video analysis

Three independent ENT specialists analyzed the video images. Deposition of dyed formulation was scored as either “head of the middle turbinate insufficiently seen” (not on the video), “absence of dye”, or “presence of dye.” Presence of dye was scored at several pre-defined locations (Table 2) and dye scoring was rehearsed to diminish inter-observer variability. Observer consensus—with at least two observers independently agreeing about deposition scoring—was used in analysis. This is a statistically valid method often used in histological grading [23]. “Non-consensus videos” were excluded from analysis. The videos in which the middle turbinate was not visible were also excluded from analysis.

## Results

Ten volunteers were included in the study: two males and eight females, median age 23 (19–28) years. Nostrils were evaluated separately ( $n=20$ ). Seven different drug-delivery techniques were compared and a total of 140 videos were analyzed. Anatomical differences were defined as “narrow valve area” (three volunteers/six

**Table 2** Deposition of dyed test formulation. Results of 140 independently reviewed nasal deposition videos. Nine pre-defined locations were assessed. Only “valid” observations (videos in which the location was visible) were assessed and scored as “dye present” or “dye absent.” A decreased amount of dye is observed when going from the vestibulum (97%) to postero-cranial locations (above the middle turbinate, 17%)

Location	Dye (%)
Vestibulum	97
Inferior turbinate head	83
Inferior turbinate tail	83
Septum	68
Lateral wall	36
Lateral of middle turbinate	28
Middle turbinate head	45
Medial of middle turbinate	30
Superior of middle turbinate	17
Median	45

nostrils), “hypertrophic or congested inferior turbinate” (ten nostrils), and “septal deviation/slight septal deviation” (five volunteers/five narrow nostrils and five contralateral “open” nostrils). Three ENT physicians, proceeding without objective measurements and without selection, independently agreed upon the interpretation of these anatomical differences. The results are presented in Table 2. Values counted as “head of the middle turbinate insufficiently seen” or without consensus (minority) were excluded from analysis (16% of all observations, mainly observations in narrow cephalic regions, only 10% in the head of the middle turbinate region). Positive scores for the overall presence of dye were found in 45% of observations, with 55% of observations resulting in negative scores (median values). On and around the middle turbinate, the number of observations without dye (55–72%) exceeded those with dye (28–45%).

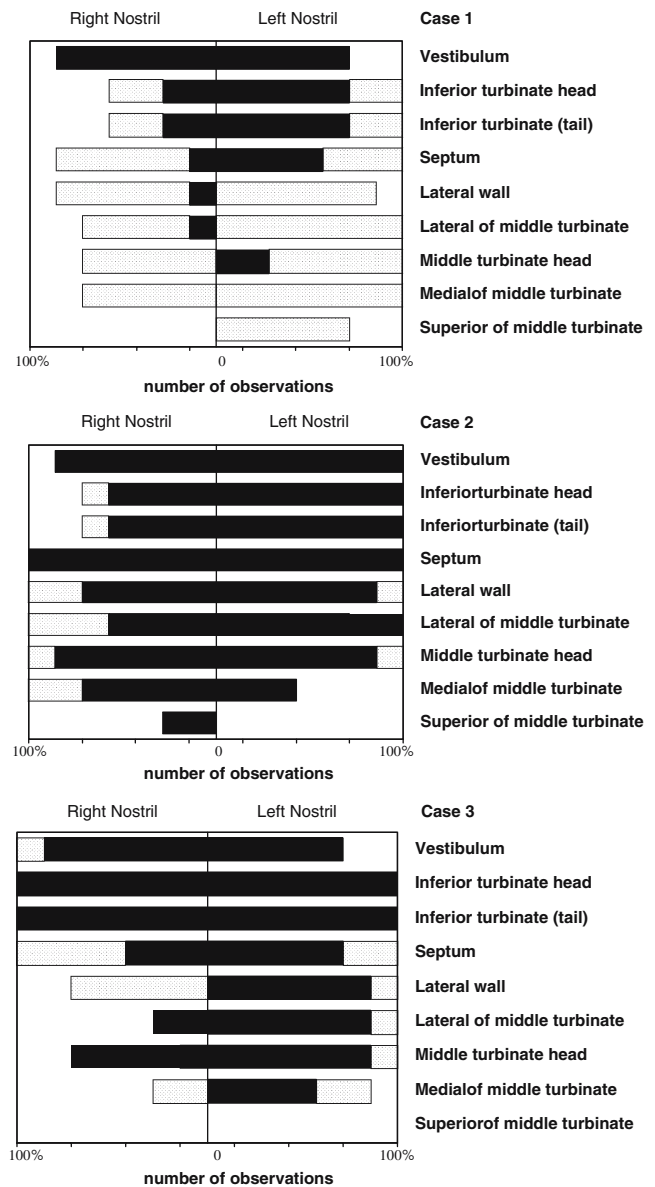
Looking at anatomical differences between individuals, a trend emerges indicating that anatomy affects the site of deposition. Figure 2a–c shows the cumulative deposition pattern in three individuals after testing all seven techniques. Only in a few techniques did the deposition reach the area around the middle turbinate, in volunteers with a narrow valve area or hypertrophic inferior turbinate (Fig. 2a). Dye deposition was good at all sites and with all techniques in volunteers with an “open” nose (Fig. 2b). A mild septal deviation caused a decrease in the amount of dye present in the area around the middle turbinate on the obstructing convex side and an increase or “normal” amount of dye on the concave side (Fig. 2c).

Head position (read: gravity) seems to have a substantial influence on drug delivery to the middle meatus. Increased amounts of dye are present in more lateral locations (this is especially important when challenging septal deviations) when using the LHL head position (Fig. 3) and in the superior region when using the HDF head position (data not shown). These results support the idea that gravity affects drug deposition.

In general, the different techniques of topical nasal drug administration were easily accepted, although most volunteers mentioned some discomfort associated with the HDF head position. This confirms the findings of Kayarkar et al. [11] The test formulation was tolerated well, but some volunteers noticed some discomfort (sneezing and itching). No adverse effects were observed.

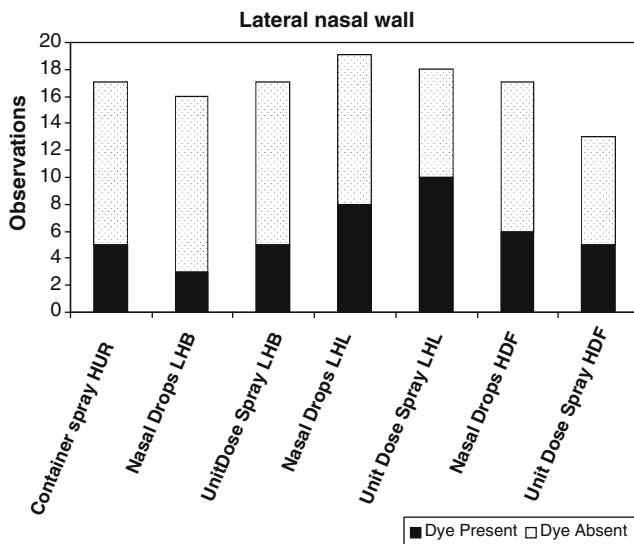
## Discussion

When the literature fails to provide definitive conclusions about the best technique for administering topical nasal drugs, it is difficult to investigate “a best technique,” even supposing that one exists. In a recent review, Aggarwal et al. [1] clearly point out why topical nasal drug deposition is hard to investigate. Individual anatomical differences, different head positions, and the use of sprays or drops all affect topical nasal drug



**Fig. 2** Individual deposition (cases 1–3) and anatomical correlation. Deposition of dye at various locations shown for both *left* and *right* nostrils of three individuals after administration using seven techniques. The presence or absence of dye per technique is cumulatively represented by a bar on the *X*-axis (100% = seven techniques). Bar length = amount of videos scored. The *white dotted bar* shows the number of videos scored as “absence of dye.” The *black bar* shows the number of videos scored as “presence of dye.” The anatomical locations are on the *Y*-axis. Each *bar* represents the percentage of observations. A clear correlation between observed deposition and anatomy can be seen. a Case 1: septal deviation to the *right*, *narrow* valve area; b case 2: an “*open* nose”; c case 3: septal deviation to the *right* and an “*open*” valve region

administration. Moreover, the wide variety of research methods used renders comparison between studies difficult. In that perspective, we have gathered data in a standardized manner relating to techniques with drops and sprays and different head positions. We studied ten



**Fig. 3** Deposition lateral nasal wall. The number of valid observations per technique is around 16/20 (84%). Dye was present on the lateral nasal wall in about 6/20 observations (36%) of these observations. The most favorable head position during administration for reaching the lateral nasal wall is lateral head low (*LHL*) (ten observations with dye present using the single-unit dose nasal spray and eight observations with dye present using nasal drops)

volunteers in an intra-individual and inter-individual comparison [14].

This pilot study establishes that individual anatomical differences, even though seeming trivial upon first inspection, explain the impossibility of identifying a single “best technique” for topical nasal corticosteroid administration [14]. The outcome of topical nasal drug treatment is even harder to predict when there are pathological changes. Obstruction by either a hypertrophic inferior turbinate or a narrow nasal valve area confines delivery of topical nasal drugs to the head of the middle turbinate (Fig. 2). These findings confirm the results of Dowley et al. [5], who showed that congestion of the inferior turbinate significantly reduced drug delivery to the middle meatus. Weber suggested that a septal deviation may affect nasal drug deposition [26], but we are not aware of any other study that investigates this suggestion. In concordance with most drug delivery studies, we excluded patients with severe septal deviations in order to ensure adequate observation of the head of the middle turbinate [5, 8–10, 24]. In spite of this exclusion criterion, we show that even slight septal deviations can have major consequences on nasal drug deposition. Only five volunteers with “minor” septal deviations were included in our study; still we were able to show that their drug deposition patterns (70 observations) are remarkably similar. Furthermore, administering topical nasal drugs in certain head positions (*LHL*, *LHB*) bypasses septal deviations, thereby increasing the amount of drug delivered to the head of the middle turbinate. Improving nasal drug deposition to the middle meatus when the individual’s anatomy is unfavorable may therefore be a matter of changing head

position. A crossover efficacy study in patients with minor effect with one head position could maybe establish the value of changing the head position. Until then it seems plausible to advise a different head position when treatment fails.

In a small study ( $n=5$ ) of Homer et al. [8], it is suggested that there is an optimal delivery technique for each individual; some volunteers do better on nasal drops whereas others are best treated with nasal sprays. In our study, we also investigated both techniques, and we conclude from our data that individual anatomical variations are the most important factor in determining the outcome of topical nasal drug treatment. In 1985, Hardy et al. [7] concluded that nasal drops are superior to nasal sprays in penetrating the nasal valve area. From our data, we conclude that considerable amounts of dye fail to penetrate the nasal valve area with all techniques and that nasal sprays are superior, albeit not significantly, to nasal drops for bypassing the valve area. The decrease in deposition toward the cephalic nasal regions (Table 2) supports the idea that the middle meatus area is difficult to reach and that most of the administered formulation will never reach this area [9, 15, 26]. It is possible that a narrow valve and vestibule hair area can be bypassed using a longer nasal-spray tip and high-velocity administration, increasing drug delivery to the head of the middle turbinate. This spray advantage is in contrast to the efficacy study of fluticasone drops of Aukema et al. [2], which seems to be more effective in the treatment of nasal polyposis when comparing the results to treatment with fluticasone *spray* as studied by Lund et al. [12] An explanation for this can be the questionable predictive value of healthy volunteers in our study.

Although we were able to investigate several aspects of nasal drug delivery, our study has several limitations: video imaging simplifies the nose to a 2D structure, it is not a quantitative measure, and the rigidity of the endoscope occasionally prevents assessment of every area of the nose. The nasal cycle (changing turbinate congestion) has not been separately taken into account. Furthermore, it is not known whether the test solution reaches the area of the middle turbinate later as a result of mucociliary clearance. This is especially important in the case of nasal drops, because droplets do not necessarily reach the target area of the middle turbinate at the same time and in the same way as nasal sprays [7]. By comparison with a recommended, more quantitative, assessment [1, 8], we did not alter nasal physiology by using a decongestant and local anesthetic. As our technique is well tolerated, repeated testing is possible, making the comparison between different techniques in one subject possible.

Although our results reveal differences in topical nasal drug deposition associated with “normal” anatomical variations, they are not statistically significant. Furthermore, in this pilot study, we did not select the patients for their nasal anatomy; we investigated whether there were correlations between anatomy and deposition in the nose. Extrapolation of our data of

healthy volunteers to patients suffering from rhinosinusitis with or without nasal polyposis is difficult, especially since intranasal deposition and distribution patterns are presumed to be different in these diseases. Investigating patients with pathological conditions like nasal polyposis should therefore be the next step in nasal drug delivery studies.

Although these results are still preliminary, we recommend taking even "minor" anatomical differences into account when trying to optimize topical nasal drug treatment for individual patients. Head position during administration should be adapted to individual anatomical characteristics. The single-unit dose spray seems to present potential advantages for topical nasal drug delivery and it therefore merits additional testing.

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## References

- Aggarwal R, Cardozo A, Homer JJ (2004) The assessment of topical nasal drug distribution. *Clin Otolaryngol* 29:201–205
- Aukema AA, Mulder PG, Fokkens WJ (2005) Treatment of nasal polyposis and chronic rhinosinusitis with fluticasone propionate nasal drops reduces need for sinus surgery. *J Allergy Clin Immunol* 115(5):1017–1023
- Benninger MS, Hadley JA, Osguthorpe JD, Marple BF, Leopold DA, Derebery MJ, Hannley M (2004) Techniques of intranasal steroid use. *Otolaryngol Head Neck Surg* 130:5–24
- Chalton R, Mackay I, Wilson R, Cole P (1985) Double-blind, placebo-controlled trial of betamethasone nasal drops for nasal polyposis. *Br Med J* 291:788
- Dowley AC, Homer JJ (2001) The effect of inferior turbinate hypertrophy on nasal spray distribution to the middle meatus. *Clin Otolaryngol* 26:488–490
- Fokkens WJ, Lund V, Bachert C, Clement P, Hellings P, Holmstrom M, Jones N, Kalogjera L, Kennedy D, Kowalski M, Malmberg H, Mullol J, Passali D, Stammberger H, Stierna P (2005) EAACI position paper on rhinosinusitis and nasal polyps executive summary. *Allergy* 60(5):583–601
- Hardy JG, Lee SW, Wilson CG (1985) Intranasal drug delivery by sprays and drops. *J Pharm Pharmacol* 37:294–297
- Homer JJ, Maughan J, Burniston M (2002) A quantitative analysis of the intranasal delivery of topical nasal drugs to the middle meatus: spray versus drop administration. *J Laryngol Otol* 116:10–13
- Homer JJ, Raine CH (1998) An endoscopic photographic comparison of nasal drug delivery by aqueous spray. *Clin Otolaryngol* 23:560–563
- Karagama YG, Lancaster JL, Karkanevatos A, O'Sullivan G (2001) Delivery of nasal drops to the middle meatus: which is the best head position? *Rhinology* 39:226–229
- Kayarkar R, Clifton NJ, Woolford TJ (2002) An evaluation of the best head position for instillation of steroid nose drops. *Clin Otolaryngol* 27:18–21
- Lund VJ, Flood J, Sykes AP, Richards DH (1998) Effect of fluticasone in severe polyposis. *Arch Otolaryngol Head Neck Surg* 124:513–518
- Mackay I (1997) Infective rhinitis and sinusitis. In: Scott Browne, *Otolaryngology* 6th edn. Butterworth Heinemann, Oxford, p 4/8/24
- Merkus P, Ebbens FA, Muller B, Fokkens WJ (2006) The "best method" of topical nasal drug delivery: a comparison of seven techniques. *Rhinology* 44:102–110
- Morén F, Bjornek K, Klint T, Wagner ZG (1988) A comparative distribution study of two procedures for administration of nose drops. *Acta Otolaryngol* 106:286–290
- Mygind N (1979) Conventional medical treatment. In: *Nasal allergy*, 2nd edn. Blackwell Scientific Publications, Oxford, pp257–270
- Parkinson SN (1933) A lateral head-low position for nasal and sinus treatment. *Arch Otolaryngol* 17:787–788
- Parkinson SN (1939) Non-traumatic ventilation treatment of the nose and sinuses. *J Laryngol Otol* 54:611–620
- Proetz AW (1926) Displacement irrigation of nasal sinuses. *Arch Otolaryngol* 4:1–13
- Proetz AW (1927) Further data on the displacement method in sinuses. *Ann Otol Rhinol Laryngol* 36:297–323
- Raghavan U, Logan BM (2000) New method for the effective instillation of nasal drops. *J Laryngol Otol* 114:456–459
- Stammberger H (1986) Endoscopic endonasal surgery: concepts in treatment of recurring rhinosinusitis. Part I. Anatomic and pathophysiologic considerations. *Otolaryngol Head Neck Surg* 94:143–147
- Tabor MP, Braakhuis BJ, van der Wal JE, van Diest PJ, Leemans CR, Brakenhoff RH, Kummer JA (2003) Comparative molecular and histological grading of epithelial dysplasia of the oral cavity and the oropharynx. *J Pathol* 199(3):354–360
- Tsikoudas A, Homer JJ (2001) The delivery of topical nasal sprays and drops to the middle meatus: a semiquantitative analysis. *Clin Otolaryngol* 26:294–297
- Weber R, Keerl R (1996) Einsatz moderner Bilddatenverarbeitung in der klinisch-rhinologischen Forschung. *Eur Arch Otorhinolaryngol Suppl* 1:271–296
- Weber R, Keerl R, Radziwill R, Schick B, Jaspersen D, Dshambazov, Mlynski G, Draf W (1999) Videoendoscopic analysis of nasal steroid distribution. *Rhinology* 37:69–73