Topical Beclomethasone in the Therapy of Smelling Disorders—A New Application Technique

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Abstract Systemic corticosteroid is the first-line-treatment for olfactory dysfunction of sinonasal origin but is afflicted with many side-effects. Topic corticosteroid does not reach the same efficacy but has a remarkable safety profile. In this trial we investigated the efficacy of topic therapy with beclomethasone (BDP) –spray. The drug was applied precisely to the olfactory cleft by a special spraying top-part. In addition we determined extinction and volume of a gelaspon sponge placed in the olfactory cleft to show the difference of the topical spray application. 18 patients with anosmia or hyposmia of different genesis and duration applied BDP-spray twice daily for four weeks. The olfactory function was determined using the TDI score ('Sniffin'-Sticks test battery'). Factors correlated with therapy efficacy were assessed. The median TDI score increased from 13.5 (0–25) at the beginning to 18.5 (1–26) after therapy of four weeks ($P = 0.005$). The extinction and volume in the moistened sponge was more than two times greater with the top-part than without. The direct application of BDP-spray to the olfactory cleft attained superior therapeutic effects than a usual applied mometasone spray, but did not perform as good as systemic corticosteroid treatment.

Keywords Corticosteroids · Beclomethasone · Olfactory dysfunction · TDI score · Olfactory cleft

Introduction

Systemically administered corticosteroid is among the most effective form of conservative treatment of olfactory dysfunction of sinonasal origin. However, the therapeutic mechanism is still being discussed [1, 2]. Peripherally, this therapy may lead to an improved function of the olfactory mucosa. Centrally, due to the decrement of thresholds of certain senses, it leads to an increased excitability. It is well known that a systemically administered corticosteroid therapy is accompanied with many side effects such as diabetes mellitus, psychogenic effects, or water retention.

On the other hand there is a therapeutic option for treating an olfactory dysfunction by applying a corticosteroid topically by means of a nasal spray. In several investigations the topic treatment did not reach the therapeutic effect or efficacy of systemically administered corticoid schemes [3, 4]. One can expect a topically applied corticosteroid, especially the newer aqueous preparations, to have a remarkable safety profile with minimal to no serious side effects [5].

Furthermore, the individual nasal anatomy and the method of application potentially affect the delivery and distribution of an intranasal applied corticosteroid [6]. In general the narrow nasal valve induces an 'orifice flow' that disrupts the air's laminar characteristics and enhances odorant mixing to improve olfactory function [5]. In the case of hyperplasia of the nasal turbinates or deviation of the nasal septum or chronic mucosal diseases this 'orifice flow' is limited. A nasal applied spray has to pass by these anatomical barriers and is knocked off especially by the ventral part of the lower turbinate.

To bypass these individual conditions, a spray applied directly to the olfactory cleft might be an adequate solution for an effective topic treatment of an olfactory dysfunction

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without developing the above mentioned side effects of systemic administered corticosteroid.

Objective

We investigated the efficacy of a topic beclomethasone therapy in patients with hyposmia and anosmia of different aetiology.

Therapeutic appendages in the treatment of olfactory dysfunction are very important, because until now there are disappointing therapy options. We investigated a new technique of corticoid application to the olfactory cleft.

Methods

Patients

In this trial 18 patients with anosmia or hyposmia of different aetiology ($n = 8$ after upper respiratory tract infection, $n = 5$ sinonasal, $n = 5$ idiopathic) were included from our Consultation Service for Olfactory Disorders (12 female/6 male; age 55.8 ± 9.6 years).

The duration of the olfactory dysfunction was median 28 months (range 2–120).

At the first consultation, a detailed case history was taken and the patients underwent an extensive ENT examination. In the nasal endoscopy the distance from the entrance of the nose to the olfactory cleft was measured and fixed with a tape on an elongated spraying top part. This top part was attached to a bottle of beclomethasone dipropionate (BDP)-spray (Fig. 1).

Again, under endoscopic control the top part was positioned to the olfactory cleft. Patients were instructed carefully how to apply the agent in a head-tipped-back position [7] (Fig. 2). Once again, the patients had to apply

the drug themselves to perform it correctly. One spray had to be applied to each nostril twice a day for four weeks.

We used a new aqueous preparation of BDP-spray with a median mass aerodynamic diameter of $2.6 \mu\text{m}$. This preparation comprises $250 \mu\text{g}$ beclomethasone per spray containing no CFCs. Beclomethasone spray is well established in the therapy of chronic rhinosininitis due to its well capacity in reducing fibroblasts [8]. Within German speaking countries (Germany, Switzerland, Austria) more than 70% of patients suffering from an olfactory dysfunction due to chronic rhinosininitis [9]. In general topic corticosteroids are a therapeutic option for the treatment of smelling disorders [10]. All patients in our investigation were highly motivated. Due to weekly calls by our Consultation Service we ensured the compliance of the patients, asked for any inconvenience and difficulties in handling and side effects and kept the patients motivation.

Extinction and volume of gelaspon sponge in the olfactory cleft

We placed an $8 \times 8 \text{ mm}$ gelaspon sponge in the bilateral olfactory cleft of a subject with a straight nasal septum after decongestion of the nasal mucosa. We then sprayed one puff of toluidine blue dye into the olfactory cleft with the special attachment on one side and without it on the other. The sponge was carefully removed under endoscopic guidance, placed in a vessel, diluted ten-fold with distilled water, mixed thoroughly, and centrifuged in an Eppendorf vessel. A photometer was used to determine extinction with an absorption maximum at 560 nm.

Olfactory function with BDP-spray

The olfactory function of our patients ($n = 18$) was determined with the 'TDI-score' at the beginning (0 weeks) and

Fig. 1 Top part and bottle of beclomethasone dipropionate (BDP) spray

Fig. 2 Application via elongated top exactly to the olfactory rim in a head-back-position

after finishing therapy (4 weeks). The TDI-score is a tripartite instrument measuring threshold, discrimination and identification with each 16 odoriferous markers ('Sniffin' Sticks test battery') [11]. Patients are partly blinded and have to make a choice ('forced choice') in this procedure to identify their olfactory function in preferably an objective manner. The TDI-score is a reliable and validated tool [12] reflecting the olfactory function. In general a score of 15 and less indicates anosmia, a score up to 30 hyposmia and above 30.5 normosmia. The change in the TDI-score was calculated, too.

Efficacy of therapy

To evaluate the efficacy of therapy in a very critical manner, we chose to compare changes of at least six points in the TDI-score. Based on previous studies [13] a change of six points results in a specified subjective improvement or deterioration of the olfactory function in the patient.

Factors associated with therapy efficacy

The correlation of the change in the TDI-score with descriptive statistics (aetiology, age, duration of disorder, gender) was assessed by a bivariate regression analysis.

Analyses

Statistical analysis was performed using SPSS (16.0, Chicago, USA). For numeric data, the Wilcoxon test was used for dependent samples, the Mann–Whitney-U and the Kruskal–Wallis test was used for independent samples. For variables according to a Gaussian distribution, the *t*-test was used. For categorical data, the chi-square test was applied. Correlations were assessed by means of bivariate regression analysis. A difference was considered significant at a *P* value of <0.05.

In case of a Gaussian distribution, the data are presented in mean and standard deviation (SD) [mean $\pm$ SD]. If not of normal distribution, the data are presented in median and its range.

Results

Extinction and volume of gelaspon sponge in the olfactory cleft

The extinction and volume in the moistened sponge were more than two times greater with the top-part than without it (Table 1). Also, the amount contained in one puff was determined to be 60 μ l with the attachment and 65 μ l without it. We were thus able to show that more dye is

Table 1 Extinction of sponge applicated with top-part (A–C) is more than two times greater

A	1.249023 ^a
B	1.266423 ^a
C	1.281923 ^a
D	0.503523 ^b
E	0.499123 ^b
F	0.486523 ^b

Photometer Spektramax M2, extinction of toluidine blue with an absorption maximum at 560 nm and temperature at 23.8°C

^a A–C sample 1 (1:10), with top-part

^b D–F sample 2 (1:10), without top-part

Fig. 3 The median TDI-score at week 0 was 13.5 (0–25) and 18.5 (1–26) at week 4, *P*= 0.006

applied to the olfactory cleft by one puff when using the special attachment. It may be assumed that the same holds true for the active agent. The subject kept its head in the same position for both applications.

Olfactory function with BDP-spray

The median TDI-score at week 0 was 13.5 (0–25) (*n* = 10 anosmia, *n* = 8 hyposmia) and 18.5 (1–26) (*n* = 7 anosmia, *n* = 11 hyposmia) at week 4 (Fig. 3). The TDI-score increased median two points (range –4.5–24; *P* = 0.006), showing a significant improvement of olfactory function after the therapy of four weeks.

Efficacy of therapy

A clinical relevant change in the TDI-Score (6 points) was seen in 4/18 (22.2%) of our patients. All of these four patients showed an improvement. Two patients had an olfactory dysfunction of sinonasal origin and the other two

had an olfactory dysfunction after an upper respiratory tract infection. 14/18 (77.8%) experienced no change. A deteriorated olfactory function was not observed in any of the patients.

Factors associated with therapy efficacy

There was no significant correlation between the change in the TDI-score and the descriptive statistics (aetiology, age, duration of disorder, gender).

Discussion

The topic corticosteroid therapy is a well-established part in the treatment of allergic rhinitis [14] and chronic sinusitis [15, 16]. Mometasone nasal spray showed the greatest effectiveness in reducing fibroblast cultures in nasal polyps followed by beclomethasone [8]. Recent results tend to prove that patients with an olfactory dysfunction after upper respiratory tract infection, idiopathic and sinonasal olfactory dysfunction benefit from a topic application of a corticosteroid, too [10, 17]. All of the published studies investigating the efficacy of a topically applied corticosteroid used ordinary applied nasal sprays discussing the best head position [7]. A direct application of a corticosteroid to the olfactory cleft via elongated spraying top part and the alteration of the olfactory function has never been reported.

In our investigation the application of BDP directly to the olfactory cleft showed a significant improvement in olfactory function after four weeks of treatment. Before treatment 10/18 (55.6%) patients suffered from an anosmia and 8/18 (44.4%) patients suffered from a hyposmia. After finishing the treatment, only seven (38.9%) patients had anosmia and 11/18 (61.1%) had hyposmia.

Considering the clinical determining change of 6 TDI-points 22% of our patients improved notable. It is, of course, not comparable to the 32% of patients who improved under a systemic corticosteroid therapy in a multicenter study [10]. However, one should not ignore the 6% of patients whose symptoms deteriorated when treated systemically in the above mentioned study.

Our four patients, who improved more than 6 TDI-points suffered from an olfactory dysfunction of sinonasal origin ($n = 2$) and of upper respiratory tract infection ($n = 2$). Of course we can not distinguish between spontaneous improvement and therapeutic effects due to our treatment in patients after upper respiratory tract infection. In the literature there are data reporting on spontaneous improvement of 1/3 [18] to 2/3 [19] of patients within one year.

None of our patients clinically worsened under the topic treatment. None of the patients reported on difficulties in

the handling. Also the patients did not report on serious side effects, apart from burning on the mucosa at the beginning of the therapy. One patient initially included did not continue therapy because of incompliance.

All together, the direct application to the olfactory cleft achieved superior therapeutic effects than a nasal spray (Nasonex[®]) but attained not as good results as a systemic treatment (tablet scheme) [10]. In the future this kind of application might be a reasonable therapeutic option or add-on-therapy especially in patients with olfactory dysfunction of sinonasal origin and after upper respiratory tract infection.

We do not report on long term effects here, because they are not yet ready for publication. In our aim, to find an adequate therapy for the treatment of smelling disorders, we are convinced of the benefits of applying agents directly on the olfactory epithelium. We think the head-position should not be a matter of discussion for the efficacy of therapy any longer. A therapy should affect the patient as less as possible and improve the smelling function as much as possible.

Conflict of interest None.

References

1. Ontjes D (1994) Adrenal corticosteroids, corticotrophin releasing hormone, adrenocorticotropin, and anti-adrenal drugs. In: Munson P (ed) Principles of pharmacology. Chapman & Hall, New York, pp 749–788
2. Meijer OC (2002) Coregulator proteins and corticosteroid action in the brain. *J Neuroendocrinol* 14:499–505
3. Blomqvist EH, Lundblad L, Bergstedt H et al (2003) Placebo-controlled, randomized, double-blind study evaluating the efficacy of fluticasone propionate nasal spray for the treatment of patients with hyposmia/anosmia. *Acta Otolaryngol* 123:862–868
4. Heilmann S, Huettenbrink KB, Hummel T (2004) Local and systemic administration of corticosteroids in the treatment of olfactory loss. *Am J Rhinol* 18:29–33
5. Benninger MS, Ahmad N, Marple B (2003) The safety of intranasal steroids. *Otolaryngol Head Neck Surg* 129:739–750
6. Scheibe M, Bethge C, Witt M et al (2008) Intranasal administration of drugs. *Arch Otolaryngol Head Neck Surg* 134:643–646
7. Benninger MS, Hadley JA, Osguthorpe JD et al (2004) Techniques of intranasal steroid use. *Otolaryngol Head Neck Surg* 130:5–24
8. Ostwald J, Graumüller S, Dommerich S et al (2003) Influence of rhinologic usual and unusual drugs on fibroblasts from nasal polyps in cell culture. *Laryngorhinootologie* 82:408–415
9. Förster G, Damm M, Gudziol H et al (2004) Olfactory dysfunction. Epidemiology, pathophysiological classification, diagnosis and therapy. *HNO* 52:679–684 Article in German
10. Heilmann S, Just T, Goektas O et al (2004) Effects of systemic or topical administration of corticosteroids and vitamin B in patients with olfactory loss. *Laryngorhinootologie* 83:729–734
11. Hummel T, Sekinger B, Wolf SR et al (1997) Sniffin' sticks: olfactory performance assessed by the combined testing of odor

- identification, odor discrimination and olfactory threshold. *Chem Senses* 22:39–52
12. Kobal G, Klimek L, Wolfensberger M et al (2000) Multicenter investigation of 1036 subjects using a standardized method for the assessment of olfactory function combining tests of odor identification, odor discrimination, and olfactory thresholds. *Eur Arch Otorhinolaryngol* 257:205–211
 13. Gudziol V, Lötsch J, Hähner A et al (2006) Clinical significance of results from olfactory testing. *Laryngoscope* 116:1858–1863
 14. Holm AF, Fokkens PJ (2001) Topical corticosteroids in allergic rhinitis; effects on inflammatory cells and mucosa. *Clin Exp Allergy* 31:529–535
 15. Lildholdt T, Rundcrantz H, Lindqvist N (1995) Efficacy of topical corticosteroid powder for nasal polyps: a double-blind, placebo-controlled study of budesonide. *Clin Otolaryngol* 20:26–30
 16. Mygind N, Lildholdt T (1996) Nasal polyps treatment: medical management. *Allergy Asthma Proc* 17:275–282
 17. Stuck BA, Blum A, Hagner AE et al (2003) Mometasone furoate nasal spray improves olfactory performance in seasonal allergic rhinitis. *Allergy* 58:1195
 18. Hummel T (2000) Perspectives in Olfactory Loss Following Viral Infections of the Upper Respiratory Tract. *Arch Otolaryngol Head Neck Surg* 126:802–803
 19. Duncan HJ, Seiden AM (1995) Long-term follow-up of olfactory loss secondary to head trauma and upper respiratory tract infection. *Arch Otolaryngol Head Neck Surg* 121:1183–1187