

THE ROLE OF TOPIC CORTICOIDS IN RHINOSINUSAL PATHOLOGY MANAGEMENT

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Abstract

Many diseases related to inflammation such as type 1 diabetes, rheumatoid arthritis and allergic diseases have increased over the past decades. Allergic diseases are more common in industrialized countries, and there is a higher rate of allergic disease in urban populations *versus* rural populations, although these differences are becoming less defined. In recent times, there have been enormous improvements in the medical practices used to treat allergic conditions. The authors take into discussion the issue of topic corticoids use and the analysis of their pharmacodynamics and bioavailability. While trying to assess the need for such therapy we appreciated the local and systemic effects of intranasal corticoid use.

Rezumat

Multe afecțiuni legate de răspunsul inflamator al organismului, cum ar fi diabetul zaharat tip I, artrita reumatoidă și bolile alergice au înregistrat o frecvență crescută în ultimii ani. Bolile alergice, inclusiv alergiile rinosinusale, sunt mai frecvente în țările industrializate, cu o diferență semnificativă între mediile urban și rural, diferență ce tinde să se estompeze. În prezent există o îmbunătățire marcată a opțiunilor terapeutice din practica medicală folosite spre a combate alergiile. Autorii iau în discuție problema utilizării corticosteroizilor topici și analizează farmacodinamia și biodisponibilitatea acestora. Pe parcursul studiului acestora au fost formulate teorii de lucru cu privire la efectele locale și sistemice ale corticoterapiei topice intranasale.

Keywords: topic corticoids, pharmacodynamics, local effects, systemic effects.

Introduction

Nasal congestion is the main symptom for the allergic rhinitis patient thus having a great impact on the quality of life. Nasal corticoids are an important component of the complex therapy of the rhino-sinus allergy.

Moderate/severe allergic rhinitis is usually hard to control without topic corticoids. The nasal administration of corticoid drugs in infants is a matter of controversy.

Allergic rhinitis has an increased prevalence through nasal and ocular manifestations. The administration of nasal corticoids tries to diminish both of the manifestations for the allergic rhinitis. There is a frequent association of the allergic rhinitis with asthma, thus needing a multidisciplinary medical approach [19]. Anti-histaminic drugs and nasal corticoids (NC) are the milestone for drug therapy in the case of allergic rhinitis despite controversies related to high systemic bioavailability, hypothalamic-pituitary-adrenal (HPA) axis suppression, reduced growth rate in children, nasal mucosa degeneration, increased intraocular pressure and cataract.

Glucocorticoids exert the systemic effects *via* glucocorticoid receptors. Fluticasone furoate is a locally active glucocorticoid that has high affinity for the glucocorticoid receptor taking over the entire lipophilic site of the receptor using hydrogen bonds. This has been proven by X-ray analysis of the fluticasone furoate crystal [20]. Further analysis showed the high affinity for glucocorticoid receptors in lungs with rapid association and slow dissociation, 30 times higher affinity in comparison to dexamethasone [18]. The relative affinity towards fluticasone receptors is higher to that of mometasone and twice of that of beclomethasone. *In vivo* and *in vitro* research revealed the efficacy of fluticasone furoate with fast translocation of receptors inside the nucleus [3, 22, 25].

The potential for systemic side effects with intranasal steroids is directly related to their systemic bioavailability. Among newer intranasal steroids, mometasone has the lowest systemic bioavailability ($\leq 0.1\%$), and thus has the lowest potential for systemic side effects. Systemic bioavailability of other intranasal steroids ranges from $<2\%$ with fluticasone propionate to 10% with budesonide, 44% with beclomethasone, and over 80% with dexamethasone.

Mometasone furoate has been undetected in as much as 98.2% of plasma samples taken from children 2 to 6 years old with allergic rhinitis after 2 hours from the last administered dose after a 42 days treatment with mometasone furoate (MF) 100 $\mu\text{g}/\text{day}$. Fluticasone furoate has a systemic bioavailability of 1.26% in some cases ($<0.3\%$), usually having a concentration of more than 500 pg/mL ; there has been only one case in which the concentration exceeded 1430 pg/mL (case study for 52 weeks) [7].

An extremely important fact for the safety of long term nasal corticoids use is the argument that it does not suppress the HPA axis. According to Brannan [4] a single dose of mometasone furoate administered intranasally at 11 PM (to maximize the potential effect on the HPA axis) at doses of 1000 μg , 2000 μg , and 4000 μg (20 times the

recommended dose in adults) were not associated with any appreciable effect on the plasma cortisol concentrations. There was no evidence of HPA axis suppression by mometasone furoate and the plasma cortisol levels after 12, 24, and 52 weeks of treatment with MF (14.45 µg/dL, 15.45 µg/dL, and 13.97 µg/dL, respectively) were similar to and not significantly different from the plasma cortisol value prior to treatment (15.34 µg/dL). These data are consistent with the virtually undetectable systemic bioavailability of mometasone furoate ($\leq 0.1\%$)[6]. The impairment of child growth has not been yet demonstrated for the last generation of topic corticoids (mometasone/fluticasone furoate) in comparison to beclomethasone bipropionate (BDP) or budesonid. The rate of growth in the BDP-treated patients was significantly slower than in the placebo patients. The mean overall rate of growth was 0.013 cm per day in the patients treated with BDP, *versus* 0.017 cm per day in the placebo patients ($p < 0.01$). Differences between treatment groups in changes from baseline height were observed after the first month of treatment ($p = 0.04$) and also at 6, 8, 10, and 12 months [23]. Single day doses of fluticasone furoate (FF) of 55 µg or 110 µg had favourable safety and tolerability profiles in children aged 2-11 years with perennial allergic rhinitis (PAR) and seasonal allergic rhinitis (SAR). Furthermore, FF showed low systemic exposure and is not associated with hypothalamic-pituitary-adrenal (HPA) axis suppression in children aged 2-11 years with PAR [14]. According to Gradman [11] fluticasone furoate has no effect on child growth but the evaluation has been made only after two weeks of treatment [13].

Materials and Methods

In the E.N.T. Department of Coltea Clinical Hospital there have been studied 148 patients, over one year of treatment with allergic rhinosinusitis in association with nasal polyps and/or asthma that were treated with fluticasone furoate (FF) and mometasone furoate (MF) (Figures 1, 2).

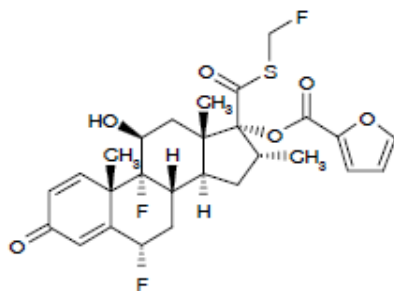
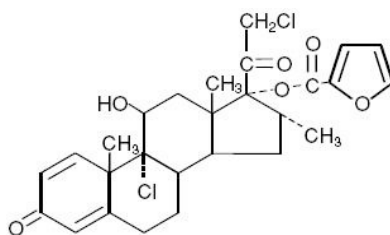


Figure 1
Fluticasone furoate

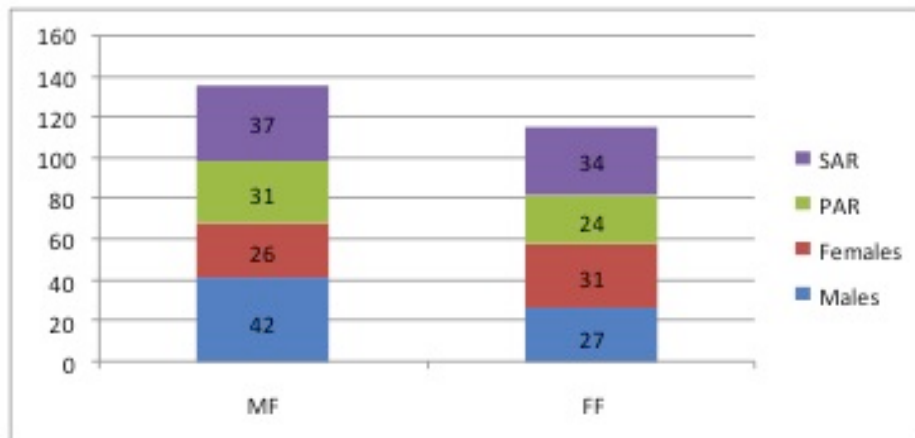
**Figure 2**

Mometasone furoate

The goal of the study was to present the results obtained after clinical reviews on patients admitted in the Ear - Nose - Throat (E.N.T.) Department of Coltea Clinical Hospital who used nasal corticoids. The main drugs were based on mometasone furoate and fluticasone furoate. There have been studied a series of factors such as efficacy, safety profile, adverse reactions of the topic nasal corticoids used. The clinical study was approved by the Ethics Committee of “Coltea” Clinical Hospital, Bucharest, Romania.

The study presents the results of the administration of topic corticoids in comparison to the literature related analysis.

The patients were divided into 3 study groups, one that underwent treatment with MF, the second group that underwent treatment with FF, and also the control group. There was no difference in response to the treatment, no matter the patients were males or females. The MF administered group included 68 patients, the FF group had 58 patients and the control group included 22 patients (Figure 3).

**Figure 3**

Study groups – seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR).

Results and Discussion

There were no severe side effects after treating the patients with either MF or FF, thus making the MF/FF therapy safe on a long-term basis.

	No. of patients (%)	
	MF 100 µg once per day (n=68)	FF 200 µg once per day (n=58)
Any side effect	32 (25%)	32 (26%)
Head ache	10 (8%)	12 (10%)
Epistaxis	4 (3%)	8 (6%)
Nasal itch	8 (6%)	4 (3%)
Pharyngitis	4 (3%)	3 (2%)
Sneeze	4 (3%)	3 (2%)

Figure 4
Side effects after MF/FF treatment

In the E.N.T. Department of Coltea Clinical Hospital we have taken biopsies from the nasal mucosa in patients with persistent allergic rhinitis and found an important decrease of the eosinophilic inflammatory infiltrate after 12 months of treatment with 100 µg/day in 104 patients, no matter what the used drug was, FF or MF. This fact allows us to advance the theory that this is a long-term low-risk efficient treatment, fact that has been postulated in other studies as well (Figures 4, 5, 6) [15].

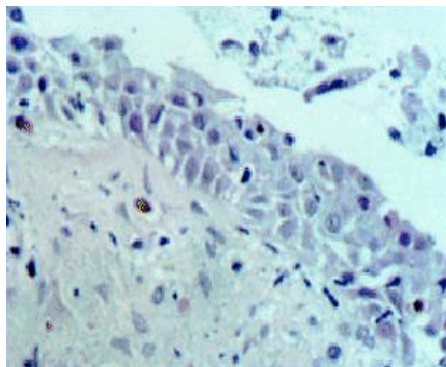


Figure 5
Nasal mucosa epithelium with extensive eosinophilic inflammatory infiltrate.

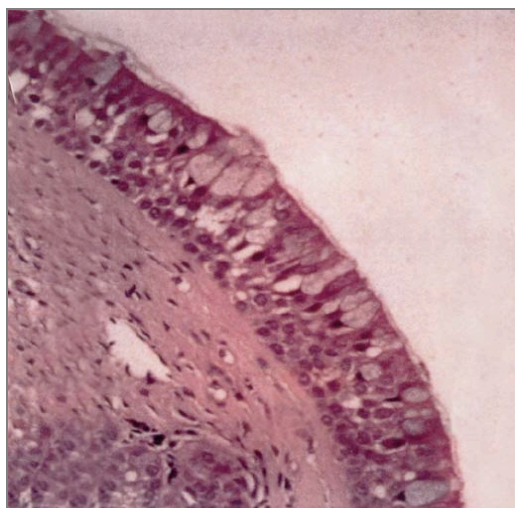


Figure 6

The absence of eosinophils after a 12 months treatment with mometasone furoate.

There are slight differences between mometasone furoate and fluticasone furoate in terms of modifications of the intraocular pressure and cataract risk. While using mometasone furoate there have been no modifications described. Fluticasone furoate can increase intraocular pressure with more than 21 mmHg in 1% of the cases and there is a high risk for cataract development [21, 12, 17].

The improvement of the symptomatology in the nasal inflammatory pathology is the main advantage of intranasal corticoids use. According to Dibildox [8] the evaluation of the subject prior to the initial pre-treatment moment showed an improvement in the overall mean score for the morning and evening measurements in a double-blind study. For the interval between the first and the 15th day there has been noticed an important decrease of patients symptoms while using mometasone furoate nasal spray compared to placebo ($p < 0.01$). The decreased symptomatology was also significant for the interval between the 16th and the 29th day of the study as well for the ending of the study in subjects treated with MF in comparison to those from the placebo group ($p < 0.01$).

In the extension phase of 26 weeks, the data regarding general status of the patients showed a tendency for progressive continuous improvement towards the end of the study. At the end of the study the average response to the MF therapy showed an important improvement of symptoms of the persistent allergic rhinitis no matter what double-blind therapy was previously conducted for each patient.

Conclusions

Intranasal corticoids have demonstrated a good safety profile in more than 15 years of clinical experience. They have multiple advantages on the available treatments for allergic rhinitis providing a strong improvement of obstruction as well as improving other allergic rhinitis related symptoms. Unlike this therapy other treatments are effective over only one of the symptoms (i.e. decongestants) or have only a moderate effect on some symptoms (i.e. antihistaminic drugs). Intranasal steroids are also the most effective therapy against inflammation which is the underlying cause of obstruction and other allergic rhinitis related symptoms. Mometasone furoate and fluticasone furoate have the lowest systemic bioavailability and the most favorable risk-benefit profiles. MF/FF proved to have few and minor side effects making them easy and safe to use in SAR and PAR treatment over long periods of time. The association between allergic rhinitis, nasal polyps and asthma is the indication for MF/FF use.

References

1. Meltzer EO - Formulation considerations of intranasal corticosteroids for the treatment of allergic rhinitis. *Ann Allergy Asthma Immunol.* 2007;98:12–21
2. Berkowitz RB, Roberson S, Zora J, Capano D, Chen R, Lutz C, Harris AG - Mometasone furoate nasal spray is rapidly effective in the treatment of seasonal allergic rhinitis in an outdoor (park), acute exposure setting. *Allergy Asthma Proc.* 1999; 20:167;
3. Biggadike K., Bledsoe R., Hassell A., Hughes S., Shewchuk, – Enhanced affinity for the glucocorticoid receptor: Receptor crystal structure and route of metabolic inactivation. 25th Congr Eur Acad Allergol Clin Immunol (June 10-14, Vienna) 2006, Abst 783.
4. Brannan MD, Herron JM, Reidenberg P, Affrime MB - Lack of hypothalamic-pituitary-adrenal axis suppression with once-daily or twice-daily beclomethasone dipropionate aqueous nasal spray administered to patients with allergic rhinitis. *Clinical Therapy* 1995;17:637-47.
5. Cutler DL, Banfield C, Affrime MB - Safety of mometasone furoate nasal spray in children with allergic rhinitis as young as 2 years of age: a randomized controlled trial. *Pediatr Asthma Allergy Immunol.* 2006;19(3):146–153.
6. Haye R, Gomez EG - A multicentre study to assess long-term use of fluticasone propionate aqueous nasal spray in comparison with beclomethasone dipropionate aqueous nasal spray in the treatment of perennial rhinitis. *Rhinology.* 1993;31(4):169–74.
7. Tai C, Wang C - Comparisons of two intranasal corticosteroid preparations in treating allergic rhinitis. Annual Meeting of the American Academy of Otolaryngology Head and Neck Surgery Foundation. 2002
8. Dibildox J. - Safety and efficacy of mometasone furoate aqueous nasal spray in children with allergic rhinitis: Results of recent clinical trials. *J Allergy Clin Immunol* 2001; 108:S54-S58.
9. Weiner JM, Abramson MJ, Puy RM - Intranasal corticosteroids versus oral H₁ receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. *BMJ* (Clinical Research Ed) 1998; 317: 1624-9.
10. Plaut M, Valentine MD - Clinical practice. Allergic rhinitis. *New England Journal of Medicine.* 2005;353(18):1934–44.

11. Salter. M., Biggadike. K., Clackers. M., Solanke. Y., Matthews. J., Maschera. B., Haase. M. – Enhanced affinity for the glucocorticoid receptor: Cellular and in vivo pharmacology. 25th Congr Eur Acad Allergol Clin Immunol (June 10-14, Vienna) 2006, Abst 781
12. Tamarcaz P., Gipson P. - Intranasal corticosteroids for asthma control in people with coexisting asthma and rhinitis. *Cochrane Database Syst. Rev.* 2003, Vol. 4;
13. Jorge Maspero, Eli Melzer, Ita Tripathy, Wei Wu, Junghee Lim, Edurad Philpot - Favourable safety and tolerability with fluticasone furoate nasal spray in children with allergic rhinitis, *World Allergy Organization Journal*, November 2007;
14. Kaliner M., Eggleston P.A., Matthews K.P. - Rhinitis and asthma. *JAMA* 1987; 258:2851-2873
15. Partridge J.J., Walker D.S. - A method for preparing fluticasone derivatives. *Drugs of the Future* 2007, 32(1): 12
16. Phillipps G.H., Bain B.M., Williamson C., Steeples I.P., Laing S.B. - Androstane 17 β -carbothioates. *Drugs of the Future* 2007, 32(1):12;
17. Steinsvag SK, Bjerknes R, Berg OH - Effects of topical nasal steroids on human respiratory mucosa and human granulocytes in vitro. *Acta Otolaryngol.* 1996;116:868–75
18. Togias A. - Rhinitis and asthma: evidence for respiratory system integration. *J Allergy Clin Immunol.* 2003;111:1171–83.

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