

Review**Long-Term Effects of Fluticasone Furoate Assessed Using Peak Nasal Inspiratory Flow in Patients with Non-Allergic Inferior Turbinate Hypertrophy**A Alper Bayram¹, Ozlem Bayram², H Huseyin Balıkcı^{3*}, M Haluk Ozkul¹, Tzema Chatzi¹, Mustafa Karakas⁴, and Mehti Salviz¹¹Department of ORL, Haseki Research and Training Hospital, Istanbul, Turkey²Department of ORL, Cankiri State Hospital, Cankiri, Turkey³Department of ORL, Burdur State Hospital, Burdur, Turkey⁴Department of ORL, Kahramanmaraş State Hospital, Kahramanmaraş, Turkey**Abstract****Aim**

To determine the long-term effects of fluticasone furoate nasal spray (FFNS) on non-allergic inferior turbinate hypertrophy (NAITH) by using peak nasal inspiratory flow meter (PNIF) results and Nasal Obstruction Symptom Evaluation (NOSE) scores.

Patients and Methods

We recruited 23 NAITH patients (10 women, 13 men) without any history of nasal surgery, allergic rhinitis or any type of nasal obstructive pathology. Patients using drugs such as antihistaminic, systemic/local decongestants and/or steroids during the last 1 year and those with upper aero digestive tract infection during the study period were excluded. Individuals under 15 or over 70 years of age were also excluded. Patients were treated with FFNS (55 µg once daily into both nasal passages) for 6 months. All patients underwent PNIF measurements and NOSE score assessments before and after 1, 3 and 6 months of treatment. The NOSE scale included five questions, which patients ranked from zero (best) to four (worst) points (total score, 0–20).

Results

The NOSE scores at 0 (pretreatment), 1, 3 and 6 months of treatment were 14.7 ± 2.62 , 10.96 ± 2.92 , 8.87 ± 2.75 and 6.74 ± 3.60 , respectively. The corresponding PNIF values were 107.61 ± 4.70 , 120.22 ± 5.66 , 132.17 ± 5.30 and 143.48 ± 4.69 l/min. Both PNIF values and NOSE scores significantly improved after treatment ($p < 0.001$).

Conclusion

FFNS is safe and effective for long-term NAITH treatment.

Keywords: Nasal Steroid; Fluticasone Furoate; Peak Nasal Inspiratory Flow; Inferior Turbinate Hypertrophy

Introduction

Inferior turbinate hypertrophy is one of the most common causes of nasal obstruction. It may be observed in allergic rhinitis, vasomotor rhinitis and chronic hypertrophic rhinitis or as a compensatory response to nasal septal deviation [1]. Various surgical techniques such as turbinoplasty, total/partial turbinectomy, chemical

cauterization, electrocauterization, laser turbinate reduction, sub mucosal tissue reduction with a microdebrider, cryotherapy and inferior turbinate radiofrequency coblation are available for the treatment of inferior turbinate hypertrophy [1-3]. Medical treatment is very effective in patients with allergic hypertrophy of the inferior turbinate, but its effectiveness in patients with non-allergic inferior turbinate hypertrophy (NAITH) is still a matter of debate [1]. Few studies have investigated the effects of nasal steroids on inferior turbinate hypertrophy [4-6]. In the present study, we investigated both subjectively and objectively, the long-term effects of fluticasone furoate nasal spray (FFNS) in NAITH patients. The objective method of evaluation consisted of peak nasal inspiratory flow meter (PNIF) measurements, and the subjective method was determination of the Nasal Obstruction Symptom Evaluation (NOSE) scale scores.

Materials and Methods

The present study was conducted on 51 NAITH patients in the Otorhinolaryngology Department of Haseki Research and Training Hospital between June 2012 and July 2013. However, 14 patients with upper aero digestive tract infections during the follow-up period, 6 patients who did not comply with the FF nose spray 2 puff (110 µg) every day during the study and 8 patients who did not regularly attend follow-up examinations were excluded from the study.

All patients underwent detailed ear–nose–throat examinations.

***Corresponding author:** HHuseyinBalıkcı, SuşehriDevletHastanesi, Kullak BurunBogazKlinigi, 58600, Suşehri, Sivas, Turkey, Fax: +90 346 311 48 03; Tel: +90 346 311 40 08; E-mail: balikcient@gmail.com

Sub Date: February 7, 2017, **Acc Date:** February 15, 2017, **Pub Date:** February 15, 2017.

Citation: A Alper Bayram, Ozlem Bayram, H Huseyin Balıkcı, M Haluk Ozkul, Tzema Chatzi (2017) Long-Term Effects of Fluticasone Furoate Assessed Using Peak Nasal Inspiratory Flow in Patients with Non-Allergic Inferior Turbinate Hypertrophy. BAOJ Aller Immunol 3: 010.

Copyright: © 2017 A Alper Bayram, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Skin-prick allergy tests were also performed in all patients. Patients with positive skin-prick allergy test results, those with negative results but with allergic symptoms except nasal obstruction such as rhinorrhea, sneezing and nasal itching, those with a history of allergic rhinitis, nasal surgery or using drugs such as antihistaminic drugs, nasal or systemic steroids and decongestant drugs, those with obstructive nasal septal deviation, sinonasal polyposis, sinonasal infections, adenoid vegetation's or nasal valve insufficiency and those who were smokers were excluded from the study. Patients with upper aero digestive tract infections during the follow-up period and those who did not regularly attend follow-up examinations were also excluded from the study. In addition, patients fewer than 15 years or over 70 years of age were not eligible to enter the study because these patients would have had difficulty in cooperating with the study protocol. The protocol of the study was approved by Haseki Research and Training Hospital Ethics Committee on June 2013. The approval identification number was 18. All patients included in the study provided written informed consent.

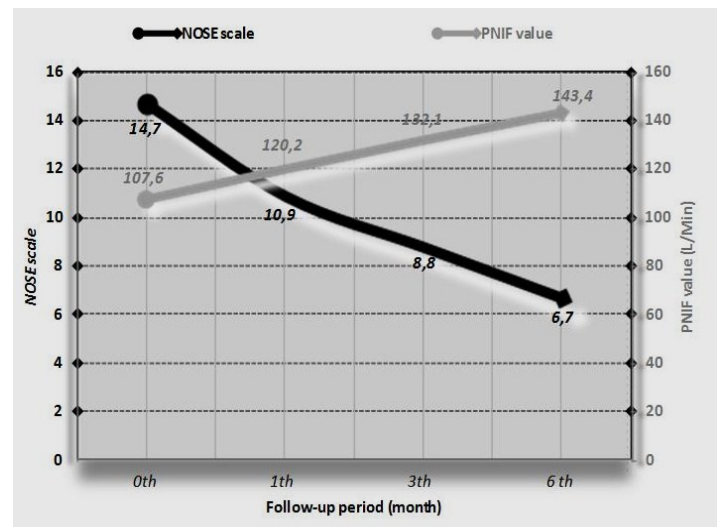
All patients were treated with FFNS at a dose of 55 µg once daily into both nasal passages for 6 months. PNIF (Clement Clarke International, Harlow, UK) measurements were made in all patients before treatment and after 1, 3 and 6 months of treatment. PNIF values during forced inspiration were expressed in liters per minute. The use of the device was explained in detail and demonstrated to all patients. The patients were asked to expire forcefully while sitting. Thereafter, with an anesthesia mask that was connected to the device placed over the mouth and nose in an airtight manner, they were asked to inspire forcefully through the nose with the lips closed. Of three consecutive measurements which differed by a maximum of 10%, the highest measurement was recorded as the final PNIF value. In addition, all patients were asked to fill the NOSE questionnaire before treatment and 1, 3 and 6 months after treatment (Figure 1). The NOSE questionnaire recorded data on the following five parameters: (i) nasal congestion or stuffiness, (ii) nasal blockage or obstruction, (iii) difficulty in breathing through the nose, (iv) difficulty in sleeping and (v) inability to breathe enough air through the nose during exercise or exertion. Patients ranked each of these parameters on a five-point

scale from zero (best) to four (worst). Thus, the total NOSE score ranged from 0 to 20. Lower scores indicated better results.

Statistical analysis of the results was performed using the Statistical Package for the Social Sciences for Windows 19.0 (Chicago, IL, USA). The paired-samples *t*-test and Mann-Whitney *U* test were used for comparisons. Correlation analysis was performed using the Pearson product-moment correlation test in the case of numerical data and using the Spearman correlation test in the case of non-numerical data. *P* < 0.05 was considered significant.

Results

The mean age of the included 23 study patients was 28.82 ± 9.64 years (range, 18–50 years); 43.5% of the patients were female, and 56.5% were male. The NOSE scores before treatment and after 1, 3 and 6 months of treatment were 14.7 ± 2.62 , 10.96 ± 2.92 , 8.87 ± 2.75 and 6.74 ± 3.60 , respectively. The differences between the pretreatment and post treatment NOSE scores were statistically significant (*p* < 0.001). The PNIF values before treatment and after 1, 3 and 6 months of treatment were 107.61 ± 4.70 , 120.22 ± 5.66 , 132.17 ± 5.30 and 143.48 ± 4.69 l/min, respectively. The differences between the pretreatment and post treatment PNIF values were statistically significant (*p* < 0.001; Figure 2). There



	Not a Problem	Very Mild Problem	Moderate Problem	Fairly Bad Problem	Severe Problem
Nasal stuffiness	0	1	2	3	4
Nasal blockage or obstruction	0	1	2	3	4
Trouble breathing through my nose	0	1	2	3	4
Trouble sleeping	0	1	2	3	4
Unable to get enough air through my nose during exercise or exertion	0	1	2	3	4

was no significant correlation between the PNIF values and NOSE scores at 0 (pretreatment), 1, 3 and 6 months ($p = 0.82$, $p = 0.14$, $p = 0.63$, $p = 0.38$, respectively). NOSE and PNIF scores, the “95 % confidence interval” for showing the margin of efficacy and

the comparison of “continuous variables” by pair t-test is showed in table 1 and 2. Moreover, neither the PNIF measurements nor the NOSE scores were significantly related with age or sex.

NOSE and PNIF scores, the “95 % confidence interval” for showing the margin of efficacy and the comparison of “continuous variables” by pair t-test is showed in table 1 and 2.

Table 1

Pairwise Comparisons

Measure:MEASURE_1

(I) factor1	(J) factor1	Mean Difference (I-J)	Std. Error	Sig. ^a	95% Confidence Interval for Difference ^a	
					Lower Bound	Upper Bound
0.month	1.month	-12,609	5,744	,234	-29,257	4,040
	3.month	-24,565*	4,157	,000	-36,616	-12,515
	6. month	-35,870*	3,395	,000	-45,710	-26,029
1.month	0.month	12,609	5,744	,234	-4,040	29,257
	3.month	-11,957	5,541	,253	-28,018	4,105
	6.month	-23,261*	5,256	,001	-38,497	-8,025
3.month	0.month	24,565*	4,157	,000	12,515	36,616
	1.month	11,957	5,541	,253	-4,105	28,018
	6.month	-11,304*	3,461	,021	-21,336	-1,273
6.month	0.month	35,870*	3,395	,000	26,029	45,710
	1.month	23,261*	5,256	,001	8,025	38,497
	3.month	11,304*	3,461	,021	1,273	21,336

Based on estimated marginal means

a. Adjustment for multiple comparisons: Bonferroni.

*. The mean difference is significant at the ,05 level.

Table 2

Pairwise Comparisons						
Measure:MEASURE_1						
(I) factor1	(J) factor1	Mean Difference (I-J)	Std. Error	Sig. ^a	95% Confidence Interval for Difference ^a	
					Lower Bound	Upper Bound
1	2	3,739*	,384	,000	2,627	4,851
	3	5,826*	,443	,000	4,542	7,110
	4	7,957*	,667	,000	6,024	9,889
2	1	-3,739*	,384	,000	-4,851	-2,627
	3	2,087*	,444	,001	,800	3,374
	4	4,217*	,613	,000	2,442	5,993
3	1	-5,826*	,443	,000	-7,110	-4,542
	2	-2,087*	,444	,001	-3,374	-,800
	4	2,130*	,484	,001	,727	3,534
4	1	-7,957*	,667	,000	-9,889	-6,024
	2	-4,217*	,613	,000	-5,993	-2,442
	3	-2,130*	,484	,001	-3,534	-,727

Based on estimated marginal means

*. The mean difference is significant at the ,05 level.

a. Adjustment for multiple comparisons: Bonferroni.

Discussion

Nasal steroids are commonly used in perennial allergic rhinitis (PAR), seasonal allergic rhinitis (SAR) and even vasomotor rhinitis or any type of non-allergic rhinitis. The positive effects of nasal steroids on nasal function have been demonstrated by many studies of allergic patients[7-9]. The effects of FFNS, a new drug molecule, on allergic rhinitis, non-allergic rhinitis and adenoid vegetation's have been demonstrated in some studies[9-13]. However, the effectiveness of FFNS in the treatment of NAITH is unproven, and this treatment may be used as an alternative to surgery[14]. Although the present study is not the first to have focused on this topic, to our knowledge, there is no identical study in the literature[4-9]. Sozen et al. compared the positive effects of nasal steroid spray and radiofrequency ablation for inferior turbinate hypertrophy and concluded that nasal steroids may be used to treat this condition[14]. However, they did not exclude patients with allergic rhinitis. In this respect, our study is unique. Our study showed that FFNS is effective on NAITH. But, we must confess as a self-criticism that the small size of the subjects without control groups in our study is a major handicap and the present study may be insufficient and may not completely prove the effectiveness of FFNS on the NAITH.

Nasal obstruction can be evaluated by subjective and objective methods. Objectively, tools such as acoustic rhinometry (AR) and rhinomanometry (RM) are used. PNIF is another objective method that is easy, cheap and non-invasive, but is not commonly used[4]. In addition, subjective tools such as the Total Nasal Symptom Score (TNSS), Visual Analog Scale (VAS) and NOSE scale can be used[10-13]. In the present study, we used PNIF for objective measurements and the NOSE scale for subjective measurements. PNIF has been compared with RM, AR and VAS in many studies and the most of them concluded that it was compatible with RM, AR and VAS [15-21]. Ozkul et al. have asserted that the normative values of PNIF must be known before the widespread use of this method[22]. They found that the normative value of PNIF in the Turkish population was 137.8 l/min (145.6 l/min in males; 130.7 l/dk in females) and that it was correlated with VAS scores[22]. Ottaviano et al. reported the normative value of PNIF as 129 l/dk in the Italian population[23]. Blomgren et al. reported the normative PNIF value as 136 l/dk in Finnish people[24]. In all these studies, the highest measurement of three consecutive measurements with a maximal difference of 10% was recorded as the final PNIF value. In the present study, the PNIF measurements taken after 3 and 6 months of treatment were approximately equal to the reported normative values. We also observed that the NOSE scores decreased with treatment.

Blomgren et al. claimed that PNIF measurements do not differ with age and sex[24]. However, Ozkul et al. and Ottaviano et al. reported that these values were affected by age and sex[22,23]. The latter result is expected because inspiratory power differs between the sexes and with age[22]. In the present study, we also observed that the PNIF measurements were significantly higher in male patients than in female patients; however, the responses to treatment were similar between the sexes.

FFNS acts by binding to an intracellular receptor and demonstrates strong anti-inflammatory effects. In vitro studies have showed that the receptor affinity of FFNS is higher than that of dexamethasone, mometasone furoate, fluticasone propionate and budesonide[25]. FFNS decreases inflammatory cells and mediators and inhibits tumor necrosis factor alpha[25]. Many studies have examined the clinical effects of FFNS. Using TNSS, Wu et al. found that FFNS at a daily dose of 110 µg for 4 weeks was effective in PAR patients[10]. Kubavat et al. evaluated 2-week-long treatments with FFNS and fluticasone propionate in patients with allergic rhinitis by using the TNSS and total ocular symptom score; they found that FFNS was more effective and well tolerated than fluticasone propionate[11]. Maspero et al. also evaluated the effectiveness of 14-day-long FFNS treatment in 1141 SAR patients, by using TNSS[13]. In another clinical study, TNSS was used to evaluate the effectiveness of FFNS in 699 patients with vasomotor rhinitis and to detect any difference between the effects of FFNS and a placebo[26]. However, all these studies were conducted on patients with allergic rhinitis. In the present study, we excluded patients with allergic rhinitis and/or allergic symptoms except nasal obstruction. We observed the long-term effects of FFNS in patients with NAITH.

Given et al. evaluated a 4-week FFNS regimen in 160 patients with allergic rhinitis by using PNIF and found that FFNS was well tolerated and effective for nasal symptoms, but not very effective for ocular symptoms[27]. In the same study, the most common side effect of FFNS was epistaxis (15%) followed by nasopharyngitis[27]. Anolik reported that the most common side effects of FFNS were (in order) headache, epistaxis, laryngopharyngeal pain, nasal ulceration and coughing[28]. In the present study, epistaxis occurred in only one of the 23 study patients after 6 months of FFNS therapy; no other side effects were observed.

Blaiss et al. and Kumar et al. reported that FFNS was more reliable than other nasal steroids because of the lower systemic absorption of the former during long-term treatment[29,30]. Fokkas et al. investigated the mucosal effects of 1-year-long FFNS therapy, and found that epithelial thickness and number of goblet cells did not change, but the number of inflammatory cells decreased after treatment[31]. Esteitie et al. reported that 2-week-long FFNS therapy decreased the level of interleukin-6, which is a proinflammatory cytokine, in adenoid tissue in children with adenoid vegetation's[32]. Our results along with those of the above studies show that FFNS can be safely used for 1 year; however, more studies are required to confirm the safety of FFNS for treatment durations of over 1 year.

Conclusion

The long-term functional effects of FFNS on non-allergic isolated inferior turbinate hypertrophy were demonstrated objectively, using PNIF and subjectively, using the NOSE scale. Both the PNIF results and NOSE scores improved significantly after 6 months of FFNS therapy. Therefore, we concluded that FFNS is effective and can be used safely in patients with isolated NAITH. However, it must be investigated on large size of subjects with control group comparison in future studies.

References

- Cingi C, Ure B, Cakli H, Ozudogru E (2010) Microdebrider-assisted versus radiofrequency-assisted inferior turbinoplasty: A prospective study with objective and subjective outcome measures. *Acta Otorhinolaryngol Ital* 30(3):138-143.
- Speciale R, Restivo S, Gallina S, Cupido G, Giammanco AM (2000) Surgery of the inferior turbinates by radiofrequency. *Otorhinolaryngologia* 50:95-98.
- Coste A, Yona L, Blumen M, Louis B, Zerah F, et al. (2001) Radiofrequency is a safe and effective treatment of turbinate hypertrophy. *Laryngoscope* 111:894-899.
- Baker DC (1979) Treatment of obstructing inferior turbinates with intranasal corticosteroids. *Ann Plast Surg* 3(3):253-259.
- Kafle P, Maharjan M, Shrestha S, Toran KC (2007) Comparison of chemical cautery (AgNO₃) and steroid spray against SMD (submucosal diathermy) in the treatment of symptomatic inferior turbinate hypertrophy (ITH). *Kathmandu Univ Med J* 5(3):335-359.
- Günel C, Başak HS (2011) [Evaluation of the effect of intranasal corticosteroid sprays on radiofrequency tissue ablation in the treatment of hypertrophied inferior turbinate]. *Kulak Burun Bogaz Ihtis Derg* 21(1):10-4.
- Aneeza WH, Husain S, Rahman RA, Van Dort D, Abdullah A, et al. (2013) Efficacy of mometasone furoate and fluticasone furoate on persistent allergic rhinoconjunctivitis. *Allergy Rhinol* 4(3):e120-6.
- Takahashi G, Matsuzaki Z, Okamoto A, Ito E, Matsuoka T, et al. (2012) A randomized control trial of stepwise treatment with fluticasone propionate nasal spray and fexofenadine hydrochloride tablet for seasonal allergic rhinitis. *Allergol Int* 61(1):155-162.
- Kumar R, Kumar D, Parakh A (2012) Fluticasone furoate: a new intranasal corticosteroid. *J Postgrad Med* 58(1):79-83.
- Wu W, Walters RD, Nadeau GA, Botnick W, Broughton N (2013) An integrated analysis of the efficacy of fluticasone furoate nasal spray versus placebo on the nasal symptoms of perennial allergic rhinitis. *Allergy Asthma Proc* 34(3):283-291.
- Kubavat AH, Pawar P, Mittal R (2011) An open label, active controlled, multicentric clinical trial to assess the efficacy and safety of fluticasone furoate nasal spray in adult Indian patients suffering from allergic rhinitis. *J Assoc Physicians India* 59:424-428.
- Han D, Liu S, Zhang Y (2011) Efficacy and safety of fluticasone furoate nasal spray in Chinese adult and adolescent subjects with intermittent or persistent allergic rhinitis. *Allergy Asthma Proc* 32(6):472-481.
- Maspero JF, Walters RD, Wu W, Philpot EE, Naclerio RM, et al. (2010) An integrated analysis of the efficacy of fluticasone furoate nasal spray on individual nasal and ocular symptoms of seasonal allergic rhinitis. *Allergy Asthma Proc* 31(6):483-492.
- Sözen E, Tansuker D, Yildrm Ö, Uçal YO, Coşkun BU (2013) Effects of radiofrequency and intranasal steroid treatments on respiratory and olfactory functions in nasal obstruction. *J Craniofac Surg* 24(3):e314-318.
- Bernmüller C, Kirsche H, Rettinger G, Riechelmann H (2008) Diagnostic accuracy of peak nasal inspiratory flow and rhinomanometry in functional rhinosurgery. *Laryngoscope* 118(4):605-610.
- Holstrom M, Scadding GK, Lund VJ, Darby YC (1990) Assessment of nasal obstruction. A comparison between rhinomanometry and nasal peak flow. *Rhinology* 28:191-196.
- Wilson AM, Sims EJ, Robb F, Cockburn W, Lipworth BJ (2003) Peak inspiratory flow rate is more sensitive than acoustic rhinometry or rhinomanometry in detecting corticosteroid response with nasal histamine challenge. *Rhinology* 41:16-20.
- Hellgren J, Jaristedt J, Dimberg L, Toren K, Karlsson G (1997) A study of some current methods for assessment of nasal histamine reactivity. *Clin Otolaryngol* 22:536-541.
- Fairley JW, Durham LH, Ell SR (1988) Correlation of subjective sensation of nasal airway – which is better?. *Clin Otolaryngol* 13:381-385.
- Wilson AM, Orr LC, Sims EJ, Lipworth BJ (2001) Effects of monotherapy with intranasal corticosteroid or combined oral histamine and leukotriene receptor antagonists in seasonal allergic rhinitis. *Clin Exp Allergy* 31:61-8.
- Day JH, Briscope MP, Rafeiro E, Ellis AK, Pettersson E, et al. (2000) Onset of action of intranasal budesonide (Rhinocort aqua) in seasonal allergic rhinitis studied in a controlled exposure model. *J Allergy Clin Immunol* 105:489-494.
- Ozkul HM, Balıkcı HH, Gurdal MM, Celebi S, Yasar H, et al. (2013) Normal range of peak nasal inspiratory flow and its role in nasal septal surgery. *J Craniofac Surg* 24(3):900-902.
- Ottaviano G, Scadding GK, Coles S, Lund VJ (2006) Peak nasal inspiratory flow; normal range in adult population. *Rhinology* 44:32-35.
- Blomgren K, Simola M, Hytonen M, Pitkaranta A (2003) Peak nasal inspiratory and expiratory flow measurements – practical tools in primary care?. *Rhinology* 41:206-210.
- Salter M, Biggadike K, Matthews JL (2007) Pharmacological properties of enhanced –affinity glucocorticoid fluticasone furoate in vitro and in vivo model of respiratory inflammatory disease. *Am J Physiol Lung Cell Mol Physiol* 293:660-667.
- Jacobs R, Lieberman P, Kent E, Silvey M, Locantore N, et al. (2009) Weather/temperature-sensitive vasomotor rhinitis may be refractory to intranasal corticosteroid treatment. *Allergy Asthma Proc* 30(2):120-127.
- Given JT, Cheema AS, Dreykluft T (2010) Fluticasone furoate nasal spray is effective and well tolerated for perennial allergic rhinitis in adolescents and adults. *Am J Rhinol Allergy* 24(6):444-450.
- Anolik R (2010) Fluticasone furoate nasal spray: Profile of an enhanced-affinity corticosteroid in treatment of seasonal allergic rhinitis. *J Asthma Allergy* 3:87-99.
- Blaiss MS (2011) Safety update regarding intranasal corticosteroids for the treatment of allergic rhinitis. *Allergy Asthma Proc* 32(6):413-418.
- Kumar R, Kumar D, Parakh A (2012) Fluticasone furoate: a new intranasal corticosteroid. *J Postgrad Med* 58(1):79-83.
- Fokkens WJ, Rinia B, van Drunen CM (2012) No mucosal atrophy and reduced inflammatory cells: active-controlled trial with yearlong fluticasone furoate nasal spray. *Am J Rhinol Allergy* 26(1):36-44.
- Esteite R, Emani J, Sharma S, Suskind DL, Baroody FM (2011) Effect of fluticasone furoate on interleukin 6 secretion from adenoid tissues in children with obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg* 137(6):576-582.