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Original Article

Effect of intranasal mometasone furoate administered in children with coexisting allergic rhinitis and asthma towards asthma attacks and lung function

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Abstract

Background Allergic rhinitis and asthma are allergic manifestations in respiratory tract, which related each other. Intranasal corticosteroid is effective in allergic rhinitis and has benefits in decreasing lower airway reactivity.

Objectives To evaluate effectiveness of intranasal mometasone furoate towards asthma in children aged 6-18 years with coexisting allergic rhinitis and asthma.

Methods A one group pretest-posttest ("before and after") study was conducted in Cipto Mangunkusumo Hospital from May to December 2008. Subjects were children aged 6-18 years, with moderate-severe intermittent or persistent allergic rhinitis with coexisting frequent episodic asthma or persistent asthma, and visited outpatient clinic of allergy immunology division or respirology division. Subjects were administered intranasal mometasone furoate 100 μg daily only for 8 weeks, without long term administration of oral and inhaled corticosteroid. Improvements in allergic rhinitis and asthma were evaluated using questionnaires and lung function tests.

Results There were 35 subjects and four of them dropped out during the study. There was >50% improvement in allergic rhinitis symptoms after 4 weeks of treatment (P<0.001). This improvement was associated with decreasing in frequency of asthma attack >50% after 8 weeks of treatment (P< 0.001). There was an insignificant improvement in FEV_1 (P=0.51). However, the evaluation of sinusitis was not performed in all subjects, thus may influence the results. During study, there were no side effects observed.

Conclusions Intranasal mometasone furoate improves allergic rhinitis and decrease >50% of asthma symptoms, however it is not followed with significant improvement in lung function. No side effects are reported during 8 weeks use of intranasal mometasone furoate. **[Paediatr Indones. 2009;49:359-64]**.

Keywords: *intranasal mometasone furoate, allergic rhinitis, asthma*

Allergic rhinitis and asthma are allergic manifestations in respiratory tract, which are related to each other.[1] Prevalence of allergic rhinitis ranges from 4.5% to 38.3% and is increasing with age. This condition is usually found in children aged more than 2 years.[2,3] Allergic rhinitis is frequently accompanied by several circumstances, such as otitis media, sinusitis, conjunctivitis, pharyngitis, dermatitis, lymphoid hypertrophy, speech disorder, sleep disorder, learning disorder, and asthma.[4] Nasal symptoms are found in 30-99% asthmatic patients, meanwhile asthma is found in 15-40% allergic rhinitis patients. United airway disease suggests similarity in morphology and physiology of upper and lower respiratory tracts.[1] Parameter to evaluate lower respiratory tract function is lung function test which can be performed in children aged more than 6 years, due to the necessity of good coordination and cooperation from the patients.[5]

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There are several medications to manage allergic rhinitis and asthma. Intranasal corticosteroid has antiinflammatory effects towards lower respiratory reactivity, e.g. the decrease of inflammation mediator from nose to lung,[6] regulation of nasobronchial réflex,[7] decrease of mouth breathing,[8] and direct effect to inflammation cells in blood or bronchus.[9] Intranasal corticosteroid is proven to be effective in managing allergic rhinitis, but its effects towards asthma still need to be evaluated. Taramarcaz et al[10] stated that intranasal corticosteroid improved asthma and forced expiratory volume in 1 second (FEV_1), but it was not statistically significant. Intranasal mometasone furoate is a potent and effective intranasal corticosteroids with minimal side effects and can be applied once daily with dose of 100 μg.[11,12]

Adequate management of allergic rhinitis may improve asthma symptoms.[13,14] Comprehensive management of allergic rhinitis and asthma is needed in order to achieve optimal quality of life. The aim of this study was to evaluate the effectiveness of intranasal mometasone furoate in patients with coexisting allergic rhinitis and asthma towards asthma symptoms and lung function.

Methods

This was a one group pretest-posttest ("before and after") study to determine the effectiveness of intranasal mometasone furoate in children with coexisting allergic rhinitis and asthma. This study was conducted from May to December 2008, at Cipto Mangunkusumo Hospital. Subjects were children aged 6-18 years, who were diagnosed with moderate-severe intermittent or persistent allergic rhinitis with coexisting frequent episodic asthma or persistent asthma, and visited outpatient clinic of allergy immunology division or respirology division. The protocol of the study was approved by the Ethical Committee of Medical School, University of Indonesia. We excluded patients who suffered from other lung disease, unable to perform lung function tests, used other long term corticosteroids, or adherence to study <75%.

Diagnosis of allergic rhinitis was based on clinical symptoms consisted of nasal symptoms induced by allergen exposure and might be accompanied with eye symptoms. According to duration of attacks, allergic rhinitis was classified into intermittent (symptoms occured less than 4 days in a week or persisted less than 4 weeks) and persistent (symptoms occured more than 4 days in a week and persisted more than 4 weeks). According to severity of symptoms, allergic rhinitis was classified into mild (normal daily activities) and moderate-severe (impaired daily activities).[15] Symptoms of allergic rhinitis were evaluated using questionnaires every 4 weeks. Parameters of clinical symptoms were evaluated, including blocked nose, sneezing, rhinorrhea, nasal itching, ear itching, eye itching, red eye, and watery eyes. Score 0 was defined if there were no symptoms, score 1: mild, score 2: moderate, score 3: severe.[16] Improvement in allergic rhinitis was evaluated by comparing the scores before and after administering the drug, and afterwards was classified into two groups, >50% and ≤50%.[14]

Diagnosis of asthma was established if there were wheezing and/or cough once or more in a month, occured for 12 months, episodic and/or chronic, nocturnal, reversible, had triggering factors, and had family history of atopy.[17] Frequent episodic asthma was defined when asthma attack occured >1 attack/month, duration of attack >1week, frequent symptoms though not under asthmatic attack. Persistent asthma was diagnosed if asthma symptoms persisted, day and night, with abnormal physical examination although not under the circumstances of asthma attack.[17] Asthma symptoms evaluated were: cough, dyspnea, wheezing, chest pain, and asthma attacks in the last 4 weeks. Severity of symptoms were evaluated using scores: score 1 for no symptoms, score 2 for symptoms occured in 1-7 days, score 3 for symptoms occured in 8-14 days, score 4 for symptoms occured in 15-21 days, score 5 for symptoms occured for 22 days or more.[18] Improvements in asthma symptoms were divided into three groups: >50%, 30-50%, and <50%.

Lung function tests were performed using spirometer with forced vital capacity. Evaluation of spirometry results, including FEV_1 comparing before and after the administration of intranasal mometasone furoate, was divided into two groups: >30% and ≤30%.[17]

Study data was processed with SPSS 16.0 statistical program, then was presented in text and tables. Statistical analysis was done with on treatment analysis using McNemar and Wilcoxon tests.

Results

We recruited 35 subjects with coexisting persistent allergic rhinitis and frequent episodic or persistent asthma; four of them dropped out. Subjects were asked to use intranasal mometasone furoate for 8 weeks and were evaluated every 4 weeks. There were 31 subjects, consisted of 21 boys and 10 girls, and most of them (21/31) were 6-12 years old. However, subjects' age ranged from 6 to 15.9 years old. All subjects had persistent allergic rhinitis, 28 subjects had frequent episodic asthma and three subjects had persistent asthma.

The duration of persistent allergic rhinitis ranged from 3 to 96 months, with the average of 28.1 months. Duration of frequent episodic asthma ranged from 4 to 84 months, with the average of 28 months. Every subject was evaluated for allergic rhinitis and asthma symptoms. Asthma attacks ranged from one to five times/month. More than 50% improvement in allergic rhinitis symptoms was found in 25/31 subjects after 4 weeks of intranasal mometasone furoate administration and in 28/31 subject after 8 weeks. Less than 50% improvement in allergic rhinitis symptoms was found in six subjects after 4 weeks and three subjects after 8 weeks ($P>0.001$), but this improvement did not become more significant until 8 weeks of intranasal mometasone furoate administration ($P=0.54$).

Asthma symptoms scores were improved after 8 weeks of intranasal mometasone furoate administration ($P>0.001$). Eleven subjects had better score after 4 weeks and the number increased to 21 subjects after 8 weeks. There were four subjects dropped out from this study. If their data were included in statistical analysis, there was no difference in the results ($P<0.05$). Improvement in asthma symptom scores was achieved in concurrence with improvement of allergic rhinitis symptoms (**Table 1**).

Besides asthma symptom score, lung functions were evaluated by comparing the FEV_1. There were 14/31 subjects having FEV_1 less than 80%. Out of 14 subjects, there was one subject having FEV_1 improvement >30% by week 4, and 12 subjects having FEV_1 improvement ≤30%. This condition persisted until week 8 ($P=0.55$). Parameter of lung functions suggested inflammation of airway, namely V_{25} and V_{50}. In this study, V_{25} and V_{50} did not significantly improve after 8 weeks of intranasal mometasone furoate administration ($P=0.63$).

The success in managing coexisting allergic rhinitis and asthma was influenced by the events of comorbidities such as sinusitis. In this study, 15 out of 31 patients were examined with nasoendocopy and seven subjects had sinusitis. All were treated with adequate antibiotics. Side effects of intranasal mometasone furoate were rare. During 8 weeks of intranasal mometasone furoate use, there was no side effect reported.

Table 1. Relationship between improvement of asthma symptoms and allergic rhinitis

Improvement of allergic rhinitis symptoms score	Improvement of asthma symptoms score			P*
	>50%	30-50%	<30%	
Week 4				
>50%	11	11	3	0.00
≤50%	0	3	3	
Week 8				
>50%	21	7	1	0.01
≤50%	0	3	0	

* Wilcoxon test

Discussion

This study was a "before and after study", that each subject became his own control. This design was chosen due to its simplicity and ability to evaluate intervention results. The limitation of this study was the occurence of bias effects and no external control group. The clinical assessment included symptoms of allergic rhinitis and asthma every 4 weeks. Triggering factors could not be entirely avoided due to incompliance and environmental condition. Co-morbidities were not evaluated in all subjects.

There were 31 subjects, consisted of 21 boys and 10 girls and majority of subjects aged 6-12 years. Twenty eight of 31 subjects had frequent episodic asthma and 3/31 subjects had persistent asthma. Prevalence of persistent asthma is rare, regarding 5% of asthma population.[17]

We observed that allergic rhinitis symptoms improved within 4 weeks of intranasal mometasone furoate use, but it became more obvious after 8 weeks

of use. There were 25 subjects whose allergic rhinitis symptoms improved >50% at the end of week 4, and it increased to 28 subjects at the end of week 8. These results were similar with studies of Weiner et al[19] and Penagos et al[20] that stated there were significant improvements of allergic rhinitis after 6-8 weeks of intranasal corticosteroid administration. Meltzer et al[14] reported 47% decrease in allergic rhinitis scores after 2 weeks of intranasal mometasone furoate administration.

The majority of subjects showed significant improvement of asthma symptoms after 8 weeks of intranasal mometasone furoate administration. Peters et al[21] and Corren et al[22] reported that intranasal corticosteroids may reduce asthma symptoms and attacks up to 50%, while Taramarcaz and Gibson[10] reported asthma symptoms improved after the administration of intranasal budesonide, but it was not statistically significant. This indicated that although the improvement of allergic rhinitis was achieved in 4 weeks of mometasone furoate use, longer period was needed to achieve the improvement of asthma. It was probably related to the remodeling process in subjects.

Various studies suggest that remodeling in asthma happens early and increases in concurrence with asthma attacks.[23-25] In this study, two subjects had >30% FEV_1 improvement at the end of week 4 and increased to four subjects at the end of week 8. There were 12/14 subjects with <30% improvement of FEV_1 at the end of week 4 and 10 of them persisted up to week 8. These results showed that eventhough the symptoms and attacks of asthma improved significantly, but there were no significant improvements of lung functions (FEV_1). The small airway inflammatory parameters, V_{25} and V_{50}, were not significantly improved (P=0.63). Inhaled corticosteroid may enhance the lower airway inflammation.[26] Reddel et al[27] reported inhaled fluticasone might improved FEV_1. Furthermore, Ramsdell et al[28] showed significant improvement of FEV_1 with the use of mometasone furoate dry powder inhaler compared with placebo (20.7% vs. 5.1%). This may related to lung deposition of inhaled corticosteroid, namely 10-50%, meanwhile the lung deposition of intranasal corticosteroid was <2%. This result indicated the improvement of asthma symptoms score was probably due to enhancement of nasal inflammation and not due to direct effects to lower airway.[9,29] Inhaled corticosteroids were needed in more severe asthma.

Along with improvement in allergic rhinitis, we were optimist in obtaining the improvement of asthma in this study, concurrent improvement of allergic rhinitis and asthma had been achieved since week 4. There were 11/31 subjects who had >50% allergic rhinitis improvement followed by >50% asthma improvement by week 4, and by week 8, there were 20/31 subjects who had >50% improvement of allergic rhinitis and asthma. By the end of week 4, there were 3/31 subjects who had ≤30% improvement of allergic rhinitis and asthma, and decreased to 0/31 by the end of week 8. Greater improvement of allergic rhinitis means greater improvement of asthma.

Asthma attacks of study subject were significantly decreased, from 2.2 to 0.3 attacks/month. Corren et al[22] stated that intranasal corticosteroids might lessen emergency visits for 50%. Peters et al[21] reported that asthma attacks were found more frequently in untreated allergic rhinitis compared to treated allergic rhinitis, i.e. 6.6% and 1.3%.

Improvements of allergic rhinitis and asthma were not accompanied by improvement of lung function. In this study, there was no relationship between the improvement of allergic rhinitis and FEV_1, by the end of week 4 (P=0.51) and week 8 (P=0.51). Taramarcaz et al[10] reported two of seven studies evaluated FEV_1 after the use of intranasal corticosteroids showed FEV_1 improvement after 6 weeks, but it was not statistically significant. Camargos et al[29] had also reported 10% FEV_1 improvement in patients who had 8 weeks of fluticasone propionate administration but it was not statistically significant. Nathan et al[30] stated in subjects with coexisting allergic rhinitis and asthma, the addition of intranasal fluticasone propionate for 4 weeks had only improved the nasal symptoms but not asthma symptoms, compared to inhaled fluticasone propionate/salmeterol in relieving asthma. This study used only intranasal mometasone furoate for 8 weeks without administration of inhaled corticosteroids and resulted in improvements of asthma without improvement of lung function. Therefore, combined and comprehensive management towards allergic rhinitis and asthma is necessary to achieve concurrent improvements in clinical symptoms and lung functions.

Subjects who did not improve in asthma symptoms and lung functions might be related to triggering factors and existing comorbidities. By the end of study, there were 21 subjects who had inevitable triggering factors, such as dusts and physical activity. Comorbidities had played important role in controlling asthma, such as sinusitis. Rachelefsky et al[13] reported 80% of treated sinusitis patients might cease the bronchodilator use and 67% of them had improvements in lung function. In this study, sinusitis was evaluated in 15 subjects and 7/15 revealed positive results from nasoendoscopic examination. All subjects experienced sinusitis were treated with antibiotics but were not analyzed due to incomplete data. Considering the strong relationship between allergic rhinitis, sinusitis, and asthma, it is better to evaluate the possibility of sinusitis accurately.

Side effects of intranasal mometasone furoate administration are rarely found. Side effects may be local or systemic. Around 10% patients experienced nasal irritation, burning sensation, and sneezing after the administration. Epistaxis is found in 2% patients.[31] Bosquet et al[15] reported that effects in hypothalamus-hypophysis-adrenal axis after 1 year use of mometasone furoate was so rare due to low systemic availability. Schenkel[32] reported that there was no growth disorder or supression of hypothalamus-hypophysis-adrenal axis after 1 year of intranasal mometasone furoate use. Meltzer et al[33] reported side effects of intranasal mometasone furoate in 20% subjects, which were headache, epistaxis, pharyngitis, cough, and nasal irritation. In this study, there was no side effect reported. Systemic effects were not evaluated due to relatively short term use and systemic availability of mometasone furoate.

We conclude that intranasal mometasone furoate can improve >50% allergic rhinitis symptoms within 4 weeks, which subsequently may reduce >50% asthma symptom but not lung function. During 8 weeks of intranasal mometasone furoate use, there are no side effects reported. We suggest to evaluate the comorbidities of allergic rhinitis, such as sinusitis so it can be treated adequately. Besides, further study is needed to evaluate improvement of lung functions with the use of both intranasal and inhaled corticosteroids in children with coexisting allergic rhinitis and asthma.

References

1. Pawankar R. Allergic rhinitis and asthma: from the link to emerging therapies. Indian J Chest Dis Allied Sci. 2003;45:179-89.
2. Scadding GK. Corticosteroids in the treatment of pediatric allergic rhinitis. J Allergy Clin Immunol. 2001;108:S59-64.
3. Kulig M, Klettke U, Wahn V, Forster J, Bauer CP, Wahn U, MAS Study Group. Development of seasonal allergic rhinitis during the first 7 years of life. J Allergy Clin Immunol. 2000;106:832-9.
4. Lack G. Pediatric allergic rhinitis and comorbid disorders. J Allergy Clin Immunol. 2001;108:S9-15.
5. Terr AI. The atopic diseases. In: Parslow TG, Stites DP, Terr AI, Imboden JB, penyunting. Medical immunology. 10th ed. Boston: McGraw Hill, 2003; p.349-69.
6. Braunstahl GJ, Overbeek SE, Kleinjan A, Prius JB, Hoogsteden HC, Fokkens WJ. Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. J Allergy Clin Immunol. 2001;1107:469-76.
7. Fontanari P, Burnet H, Zattara-Harmann MO, James Y. Changes in airway resistance induced by nasal inhalation of cold dry, dry, or moist air in normal individuals. J Appl Physiol. 1996;81:1739-43.
8. Henriksen JW, Wenzel A. Effect of an intranasally administered corticosteroid (budesonide) on nasal obstruction, mouth breathing and asthma. Am Rev Respir Dis. 1984;130:1013-8.
9. Watson WIA, Becker AH, Simon FER. Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma: effect on lower airway responsiveness. J Allergy Clin Immunol. 1993;91:97-101.
10. Taramarcaz P, Gibson PG. Intranasal corticosteroids for asthma control in people with coexisting asthma and rhinitis. [Cochrane review]. In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software.
11. 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:S54-8.
12. Trangsrud AJ, Whitaker AL, Small RE. Intranasal corticosteroids for allergic rhinitis. Pharmacotherapy. 2002;22:1458-67.
13. Rachelefsky GS, Katz RM, Siegel SC. Chronic sinus disease with associated reactive airway disease in children. Pediatrics. 1984;73:526-29.
14. Meltzer EO, Jalowayski AA, Orgel A, Harris AG. Subjective and objective assessments in patients with seasonal allergic

rhinitis: effects of therapy with mometasone furoate nasal spray. J Allergy Clin Immunol. 1998;102:39-49.
15. Bousquet J, van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. ARIA workshop report. J Allergy Clin Immunol. 2001;108:S147-276.
16. Bronsky E, Boggs P, Findlay S, Gawchik S, Georgitis J, Mansmann H, dkk. Comparative efficacy and safety of a once-daily loratadine-pseudoephedrine combination versus its components alone and placebo in the management of seasonal allergic rhinitis. J Allergy Clin Immunol. 1995;96:139-47.
17. UKK Pulmonologi. Pedoman nasional asma anak. In: Rahajoe N, Supriyatno B, Setyanto DB, editors. Jakarta: PP IDAI, 2004; p. 1-44.
18. Pediatric asthma symptom score [homepage on the internet]. c2000 [cited 2007 Nov 15]. Available from: http://www.rand.org.
19. Weiner JM, Abramson MJ, Poy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomized controlled trials. BMJ. 1998;317:1624-9.
20. Penagos M, Compalati E, Tarantini F, Baena-Cagnani CE, Passalacqua G, Canonica GW. Efficacy of mometasone furoate nasal spray in the treatment of allergic rhinitis: meta-analysis of randomized, double blind, pacebo-controlled, clinical trials. Allergy. 2008;63:1280-91.
21. Peters JC, Neslusan C, Crown WH, Torres A. Treating allergic rhinitis in patients with comorbid asthma: the risk of asthma-related hospitalizations and emergency department visit. J Allergy Clin Immunol. 2002;109:57-62.
22. Corren J, Manning BE, Thompson SF, Hennesy S, Strom B. Rhinitis therapy and the prevention of hospital care for asthma: a case control study. J Allergy Clin Immunol. 2004;113:415-9.
23. Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. Asthma, from bronchoconstriction to airways inflammation and remodeling. Am J Respir Cri Care Med. 2000;161:1720-45.
24. Jeffery PK, Haahtela T. Allergic rhinitis and asthma: inflammation in one-airway condition. BMC Pulm Med. 2006;6:S5-16.
25. Payne DNR, Rogers AV, Adelroth E, Bandi V, Guntupalli KK, Bush A, dkk. Early thickening of the reticular membrane in children with difficult astnma. Am J Respir Crit Care Med. 2003;167:78-82.
26. Mauad T, Bel EH, Sterk PJ. Asthma therapy and airway remodeling. J Allergy Clin Immunol. 2007;120:997-1009.
27. Reddel HK, Belousova EG, Marks GB, Jenkins C. Does continuous use of inhaled corticosteroids improve outcomes in mild asthma? A double-blind randomized controlled trial. Prim Care Respir J. 2008;17:39-45.
28. Ramsdell JQ, Nayak AS, Bensch GW. Efficacy of treatment with oncedaily evening dosing of mometasone furoate dry powder inhaler 200 micrograms in asthma stratified by baseline severity. Am J Respir Crit Care Med. 2009;179:19-24.
29. Camargos P, Ibiapina C, Lasmar I, Cruz AA. Obtaining concomitant control of allergic rhinitis and asthma with a nasally inhaled corticosteroid. Allergy. 2007;62:310-6.
30. Nathan RA, Yancey SW, Waitkus-Edwards K, Prillaman BA, Stauffer JL, Philpot E, et al. Fluticasone propionate nasal spray is superior to montelukast for allergic rhinitis while neither affects overall asthma control. Chest. 2005;128:1910-20.
31. Lumry WR. A review of the preclinical and clinical data of newer intranasal steroids used in the treatment of allergic rhinitis. J Allergy Clin Immunol. 1999;104:150-8.
32. Schenkel EJ, Skoner DP, Bronsky EA, Miller SD, Pearlman DS, Rooklin A, et al. Absence of growth retardation in children with perennial allergic rhinitis after one year of treatment with mometasone furoate aqueous nasal spray. Pediatrics. 2000;105:22-9.
33. Meltzer EO, Berger WE, Berkowitz RB, Bronsky EA, Dvorin DJ, Finn AF, et al. A dose-ranging study of mometasone furoate aqueous nasal spray in children with seasonal allergic rhinitis. J Allergy Clin Immunol. 1999;104:107-14.