Investigation of the efficacy of generic and brand-name salmeterol/fluticasone combination in the management of asthma: a randomized comparative trial

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Summary. Background: Asthma is the most chronic inflammatory disease of the airways worldwide. Combination therapy with inhaled fluticasone and salmeterol is a common practice for the long-term management of asthma. Seretide® and Fluticort plus® are two available generic and brand name products of salmeterol/fluticasone. This study aimed to compare the efficacy and safety of these two drugs. Materials and Methods: In this randomized comparative, clinical trial, 80 asthmatic patients were allocated to Fluticort plus® (n=40) or Seretide® (n=40) for a period of 4 weeks. Patients with mild asthma were instructed to inhale one puff each 12 hours and those with moderate asthma two puffs every 12 hours. Respiratory volumes (assessed using spirometry), quality of life (assessed using St. George’s Respiratory Questionnaire [SGRQ]) and control of asthmatic symptoms (assessed using asthma control test [ACT]) were evaluated at baseline and at the end of the study. Results: ACT score improved only in the Fluticort plus® group (p=0.012) while it was not significantly changed in the Seretide® group (p=0.178). In both treatment groups, FEV1, FEV1/FVC, and total as well as subscale SGRQ scores were significantly improved by the end of the study (p<0.05). Seretide® more efficiently improved respiratory volumes and SGRQ score in comparison with Fluticort plus® (p<0.05). Conclusion: Our comparative trial indicated that generic fluticasone/salmeterol product could improve respiratory volumes, quality of life but its efficacy is lower than the brand-name product. However, Fluticort plus® improved asthma control more efficiently compared with Seretide®. (www.actabiomedica.it)

Key words: asthma, fluticasone propionate, salmeterol xinafoate, Flucort plus®, Seretide®, generic, brand

Introduction

Asthma is the most common chronic respiratory disease worldwide. According to WHO estimates, 255,000 people died because of asthma in 2005 and currently 235 million people have asthma. Available evidence shows that 8% of the population in the Eastern Mediterranean Region including Iran suffer from asthma and over 80% of deaths because of asthma occur in developing countries (1). Asthma is characterized with inflammatory airflow obstruction leading to shortness of breath, chest tightness, wheeze and coughs. Chronic airway inflammation causes airway hyper-responsiveness. This hyper-responsiveness is triggered by environmental factors such as cold air, allergens and smoking, leading to reversible obstruction (2).

Asthma is not curable but appropriate management can significantly contribute to the control of symptoms and complications, and improvement of life...
quality. Bronchodilators are a major class of medica-
tions for asthma owing to their capacity to relax airway
smooth muscles and causing a rapid relief. The most
extensively used inhaled bronchodilators are -adrener-
gic agonists that are available in short-acting (SABA
e.g. salbutamol) and long-acting (LABA e.g. salmeter-
ol) forms. Another important class of anti-asthmatic
medications are anti-inflammatory agents that miti-
gate airway inflammation. The most commonly used
anti-inflammatory drugs are inhaled corticosteroids
(ICS) (3). It has been proved that combination therapy
with LABAs and ICSs reduces the frequency and se-
verity of asthmatic exacerbations, and improves long-
term treatment more efficiently compared with ICSs or
LABAs alone (3-7). Moreover, concurrent administra-
tion has additional benefits in terms of cost and pa-
tient compliance, and has been recommended by the
main available guidelines (8). Salmeterol/fluticasone is
one of the most widely used combinations of this type
and is FDA-approved. This combination is available
in a single inhaler as a commercial brand-name (Sere-
tide®) and generic (Fluticort plus®) products in Iran.
Seretide® is marketed by GlaxoSmithKline (UK), and
is more expensive than the generic product, Fluticort
plus®, which is marketed by Medispray (India). With
regard to the expiration of Seretide® patent in 2010,
development of generic products provides an oppor-
tunity for increasing the availability of the drug, and
reducing the consumer’s costs. However, conducting
comparative trials is a necessary step to confirm the
efficacy and safety of generic products. In this study,
we aimed to compare the efficacy and safety of brand-
named and generic products of salmeterol/fluticasone in
patients suffering from asthma.

Material and methods

Subjects

This study was designed as a pilot randomized
comparative trial. Out of 120 initially asthmatic sub-
jects referred to the Respiratory Clinic of the Baqi-
yatallah Hospital (Tehran, Iran), 102 subjects were
selected based on inclusion and exclusion criteria and
randomized to receive either 250 microgram Fluticort
plus® (n=51) or Seretide® (n=51). Each puff of Flu-
ticort plus® or Seretide® inhaler contains 25 micro-
grams of salmeterol and 250 microgram of fluticasone.
Inclusion criteria were age between 30 and 70 yrs,
diagnosis of mild to moderate asthma (according to
clinical symptoms and spirometry) (9), no need for
hospitalization, not being under concurrent treatment
with other medications including agonists and corti-
costeroids, and absence of Fluticort plus® or Sere-
tide® contraindication. Exclusion criteria were history
of systemic diseases, or cigarette smoking. Also, not
consuming the allocated drug for more than 48 hours
was considered as a criterion for being considered as
“drop out”. Each patient was aware of the type of drug
he/she was receiving during the study. The study pro-
tocol was approved by the Ethics committee of the
Baqiyatallah University of Medical Sciences and writ-
ten informed consent was obtained from the partici-
pants.

Treatment

Patients with mild asthma were instructed to in-
hale one puff each 12 hours and those with moderate
asthma two puffs every 12 hours. Treatment duration
in both groups was 4 weeks. During the study, treat-
ment of patients in both groups was according to the
Global Strategy for Asthma Management (GINA)
guideline (10).

Evaluation

Pulmonary function, control of symptoms and
quality of life were evaluated at baseline and after 4
weeks of treatment in both groups. To assess pulmo-
nary function, forced expiratory volume in the first
second (FEV1), forced vital capacity (FVC), and FEV1/
FVC ratio were measured using a Vmax20 spiromeer
(Chest Co., Italy). The spirometer was calibrated using
a device provided by the manufacturer.

To assess asthma control, asthma control test
(ACT) was performed. ACT is a quick numerical test
for asthmatic patients 12 years and older. Its validity
and reliability has been approved in different popula-
tions (11-14). The test includes 5 questions which ask
how often the patient has symptoms, how often has
used rescue inhaler or nebulizer, how much of the time asthma kept the patient from getting as much done at work, school or home, and how the patient rates his/her asthma control during the past 4 weeks. A total score of 19 or less out of 25 demonstrates lack of proper control of asthma (15).

Quality of life was evaluated using St. George’s Respiratory Questionnaire (SGRQ). Patients answered SGRQ (after receiving instructions about how to fill the questionnaire) in a calm place independently, in the presence of an observer. SGRQ has 76 items categorized in three subscales: “symptoms” subscale which asks about respiratory symptoms, their frequency and severity; “activity” subscale which asks about activities that cause or are limited by dyspnea and “impacts” subscale which asks about social functioning and psychosocial disorders due to lung disease. The overall score ranges between 0 to 100, and higher scores indicate a more severe impairment. SGRQ has been reported to be a sensitive, repeatable and numerical tool for evaluation of a range of disorders affecting quality of life in patients with respiratory diseases (16).

Statistical analysis

Data were analyzed using the SPSS software, version 18.0. Within-group comparisons were made using paired samples t-test (for normally distributed data) or Wilcoxon signed-ranks test (for non-normally distributed data). Comparisons of baseline and post-treatment values between the study groups was carried out using independent samples t-test (for normally distributed data) or Mann-Whitney U test (for non-normally distributed data). Comparison of categorical variables between the two groups was made using the Fisher’s exact test. A two-sided p-value of <0.05 was considered as statistically significant.

Results

Flow of participants

Out of the 102 randomized asthmatic patients, 80 (40 in each group) completed the study. The reasons for drop outs were nasal dryness (4 subjects in the Fluticort plus® and 3 in the Seretide® group) and non-compliance with the study medications (7 subjects in the Fluticort plus® and 8 in the Seretide® group) (Figure 1). The number of drop-outs was not significantly different between the study groups (p>0.05). Study groups were statistically comparable regarding age, gender, weight and disease duration (Table 1).

Spirometry

All three measured spirometric indices namely FEV1 (p<0.001 in both groups), FVC (p=0.034 in the Fluticort plus® and p<0.001 in the Seretide® group) and FEV1/FVC (p<0.001 in both groups) were significantly increased following 4-week treatment with either of the study medications. Between group comparisons revealed that although FEV1 (p=0.306) and FEV1/FVC ratio (p=0.212) were comparable between the groups at baseline, FVC was higher in the Fluticort plus® group (p=0.001). On-treatment comparisons showed significantly higher values of FEV1 (p=0.029) and FEV1/FVC (p=0.004) in the Seretide® versus Fluticort plus® group, while FVC was comparable between the groups (p=0.068) (Table 2).

ACT

As shown in Table 3, mean ACT score was significantly increased by the end of trial in the Fluticort plus® (p=0.012) but not Seretide® group. Neither baseline (p=0.356) nor on-treatment scores (p=0.187) were significantly different between Fluticort plus® and Seretide® groups (p>0.05).

SGRQ

Total and subscale SGRQ scores were lower in the Fluticort plus® group at baseline, while on-treatment scores were higher compared with the Seretide® group. In both study groups, 4 weeks of treatment resulted in a significant improvement in the quality of life according to both total SGRQ score and subscale scores of symptoms, impact and activity (Table 3). The only exception was a significant increase in the impact subscale score in Fluticort plus® group (p<0.001).
No severe adverse event was reported in either of the study groups during the trial. There were 4 reports of nasal dryness in the Fluticort plus® and 3 in the Seretide® group. Overall, neither the frequency of reported adverse events nor the number of non-compliant subjects and drop-outs was significantly different between Fluticort plus® and Seretide® groups ($p>0.05$).

**Table 1. Baseline characteristics of the study groups**

| Characteristics         | Fluticort plus® | Seretide® | $p$-value |
|-------------------------|----------------|-----------|-----------|
| Age (yrs)               | 47.87±11.35    | 48.35±10.55 | 0.847     |
| Female (n)              | 21             | 19        | 0.823     |
| Weight (Kg)             | 72.35±18.3     | 73.8±6.10 | 0.636     |
| Height (cm)             | 167.25±10.27   | 173.3±7.15 | 0.003     |
| Disease duration (yrs)  | 4.5±1.76       | 3.92±1.88 | 0.164     |

Values are expressed as mean ± SD or number.

**Discussion**

Replacement of brand-name and generic drugs is a viable strategy to reduce the rising healthcare costs. In addition to the observation of standards in terms of content (active pharmaceutical ingredient and excipients), labeling and manufacturing, the efficacy, safety and quality of a generic drug must be equal to those of the brand-name drug in order to allow a bioequivalence judgment (17, 18). The motivation to reduce treatment costs through prescription of generic drugs has made healthcare systems in many countries, including Iran, to adopt generic policy (19-21). Bioequivalence of a generic drug with its brand-name counterpart must be demonstrated by appropriately designed randomized controlled trials and bioavailability studies to evaluate the non-inferiority of the generic product with regard to its efficacy and safety (22-29).

Asthma is the most common chronic respiratory disease worldwide and 80% of deaths due to asthma...
occurs in low- and middle-income countries. Hence, development of generic products with lower price, wider availability and equivalent safety and efficacy compared with the brand-name drugs might be a solution to provide asthmatic patients with proper treatment. Seretide®, a brand-name product, is the most common combinatory inhaler used in asthma management, and contains both ICs (fluticasone) and LABA (salmeterol).

This results of this study indicated that Fluticort plus®, as a generic product, improves spirometric function, quality of life and respiratory symptoms (according to the ACT scale) in asthmatic patients with mild to moderate disease. However, the degree of improvement in spirometric function and quality of life was found to be greater with Seretide®. In a previous study, Maneechotesuwan et al. investigated the anti-inflammatory effects of salmeterol/fluticasone combination on sputum eosinophil count and fractional exhaled nitric oxide as primary and secondary outcomes, respectively. The results did not suggest any significant difference between generic and brand-name products in controlling asthmatic symptoms following 4 weeks of treatment (30). It is worth noting that in the present study, SGRQ total and subscale scores as well as FVC were significantly lower in the Fluticort plus® versus Seretide® group at baseline, and this might have partially confounded the above-mentioned results.

The present study has some limitations that deserve to be mentioned. First, this study was performed in a pilot scale and with a short-term duration of follow-up, and hence longer term studies are required to provide insight with respect to the comparative efficacy of drugs on asthma exacerbations. In addition, the findings of this study could provide useful information for the determination of size and equivalence margin

| Variables | Fluticort plus® | Seretide® |
|-----------|----------------|-----------|
| **FEV1**  | Pre 71.77±6.06 Post 85.15±8.6 | Pre 70.35±6.29 Post 89.57±9.11 |
| **FVC**   | Pre 75.62±7.25 Post 80.62±8.23 | Pre 71.0±4.91 Post 84.97±12.35 |
| **FEV1/FVC** | Pre 73.72±5.02 Post 82.37±8.28 | Pre 72.17±5.96 Post 87.9±8.27 |

FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity.
1 Comparison between the two groups before treatment
2 Comparison between the two groups after treatment

| Variables | Fluticort plus® | Seretide® |
|-----------|----------------|-----------|
| **ACT**  | Pre 18.55±2.25 Post 23.42±3.32 | Pre 23.27±3.21 Post 24.22±1.83 |
| **SGRQ** |                      |               |
| Symptoms  | Pre 18.9±4.13 Post 12.95±2.84 | Pre 26.1±9.50 Post 7.27±1.81 |
| Impact   | Pre 8.55±1.19 Post 14.1±11.99 | Pre 18.47±7.45 Post 6.85±1.65 |
| Activity | Pre 21.2±3.5 Post 15.07±3.63 | Pre 23.4±5.05 Post 13.27±2.45 |
| Total    | Pre 27.15±5.13 Post 17.0±3.57 | Pre 31.55±3.98 Post 14.40±2.71 |

ACT: asthma control test; SGRQ: St. George’s Respiratory Questionnaire.
1 Comparison between the two groups before treatment
2 Comparison between the two groups after treatment

Table 2. Respiratory volumes before and after treatment with study drugs

Table 3. ACT and SGRQ scores before and after treatment
in future trials. Second, the study population was limited to patients with mild to moderate asthma and it is unclear whether the efficacy of generic and brand-name drugs is different in controlling more severe asthmatic symptoms. Third, the adherence to treatment, although being comparable between the study groups, was relatively low. Fourth, some of the parameters including SGRQ and FVC scores were different between the groups at baseline. Finally, antioxidant intake at baseline and during the period of study was not assessed. Owing to the documented role of oxidative stress in promoting airway inflammation and asthma severity (31, 32), between-group differences in antioxidant intake might have confounded the results.

In summary, the results of this comparative trial favored a higher efficacy of brand-name salmeterol/fluticasone versus the generic product, though the products were comparable in terms of safety. Since the disease symptoms and quality of life were improved by both products, the generic drug could be used as a cheaper treatment in asthmatic patients with mild to moderate symptoms. Nevertheless, future non-inferiority trials are required to compare the efficacy and safety of generic and brand-name drugs on a long-term basis.

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References

1. Woo J, Kim HY, Byun BJ, Chae CH, Lee JY, Ryu SY, et al. Biological evaluation of tanshindiols as EZH2 histone methyltransferase inhibitors. Bioorganic and Medicinal Chemistry Letters 2014; 24(11): 2486-92.
2. Rees J, Kanabar D, Pattani S. ABC of Asthma: Wiley; 2010.
3. Longo D, Fauci A, Kasper D, Hauser S, Jameson J, Loscalzo J. Harrison’s Principles of Internal Medicine, 18th Edition: McGraw-Hill Education; 2011.
4. Gibson PG, Powell H, Ducharme FM. Differential effects of maintenance long-acting β-agonist and inhaled corticosteroid on asthma control and asthma exacerbations. Journal of Allergy and Clinical Immunology 2007; 119(2): 344-50.
5. Woodcock A, Bagdonas A, Boonsawat W, Gibbs M, Bouquet J, Bateman E. Improvement in asthma endpoints when aiming for total control: salmeterol/fluticasone propionate versus fluticasone propionate alone. Prim Care Respir J 2007; 16(3): 155-61.
6. Bateman E, Bouquet J, Busse W, Clark T, Gul N, Gibbs M, et al. Stability of asthma control with regular treatment: an analysis of the Gaining Optimal Asthma control (GOAL) study. Allergy 2008; 63(7): 932-8.
7. Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. Cochrane Database Syst Rev. 2010; 5(5).
8. Turner S, Paton J, Higgins B, Douglas G. British guidelines on the management of asthma: what’s new for 2011? Thorax. 2011: thoraxjnl-2011-200213.
9. National Heart L, Institute B. Asthma care quick reference: Diagnosing and managing asthma. US Department of Health and Human Services National Institute of Health: Bethesda, MD Retrieved on February 2012; 20: 2014.
10. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. The European respiratory journal 2008; 31(1): 143-78.
11. Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA, et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. Journal of Allergy and Clinical Immunology 2006; 117(3): 549-56.
12. Grammatopoulou EP, Stavrou N, Myrianthefs P, Karteriotis K, Baltopoulos G, Behrakis P, et al. Validity and reliability evidence of the Asthma Control Test-Act in Greece. Journal of Asthma 2011; 48(1): 57-64.
13. Vega J, Badia X, Badiola C, López-Viña A, Olaguibel J, Picado C, et al. Validation of the Spanish version of the Asthma Control Test (ACT). Journal of Asthma 2007; 44(10): 867-72.
14. Zhou X, Ding F-M, Lin J-T, Yin K-S. Validity of asthma control test for asthma control assessment in Chinese primary care settings. CHEST Journal 2009; 135(4): 904–10.
15. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. Journal of Allergy and Clinical Immunology 2004; 113(1): 59–65.
16. Jones PW, Quirk F, Baveystock C. The St George’s respiratory questionnaire. Respiratory medicine 1991; 85: 25–31.
17. Dunne S, Shannon B, Dunne C, Cullen W. A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study. BMC Pharmacology and Toxicology 2013; 14(1): 1.
18. Keith LG, Oleszczuk JJ, Stika CS, Stine S. Generics: what’s in a name? International journal of fertility and women’s medicine 1997; 43(3): 139–49.
19. Nelson S, Slørød L, Spigset O. Generic drugs instead of
brand drugs prescriptions--long overdue. Tidsskrift for den Norske laegeforening: tidsskrift for praktisk medicin, ny raekke. 2006;126(4):441-3.
20. Zargarzadeh A, Emami M, Hosseini F. DRUG-related hospital admissions in a generic pharmaceutical system. Clinical and Experimental Pharmacology and Physiology 2007; 34(5-6): 494-8.
21. Dupont A, Heller F. Generics and cost-effective prescribing in Belgium: does bioequivalence always translate in therapeutic equivalence? Acta Clinica Belgica 2009; 64(5): 406-14.
22. Beiraghdar F, Panahi Y, Einollahi B, Nemati E, Ghadiani MH, Sahebkar A, et al. Investigation of the efficacy of a biogeneric recombinant human erythropoietin alfa in the management of renal anemia in patients on hemodialysis: a multi-center clinical trial. Clinical laboratory 2011; 58(7-8): 737-45.
23. Beiraghdar F, Panahi Y, Einollahi B, Torkaman M, Mohammadi R, Marzony ET, et al. Investigation of the efficacy of a biogeneric recombinant human erythropoietin alfa in the correction of post-transplantation anemia: a randomized comparative trial with Eprex. Clinical laboratory 2011; 58(11-12): 1179-85.
24. Sayyah M, Argani H, Pourmand G, Amini H, Ahmadian A, editors. Pharmacokinetics, efficacy, and safety of iminoral compared with neoral in healthy volunteers and renal transplant recipients. Transplantation proceedings, 2007: Elsevier.
25. Kazemifard AG, Moore DE, Mohammadi A. Polargraphic determination of benzaldehyde in benzyl alcohol and sodium diclofenac injection formulations. Journal of pharmaceutical and biomedical analysis 2002; 30(2): 257-62.
26. Heshmat R, Taheri E, Larjiani B. Comparison of a generic and a brand metformin products in type II diabetes: A double blind randomized clinical trial study. DARU Journal of Pharmaceutical Sciences 2007; 15(2): 113-7.
27. Aleyasin A, Hanafi S, Saffarieh E, Torkamandi H, Allahyari S, Sadeghi F, et al. Efficacy of generic granisetron vs Kytril® for PONV in major gynecological operations: a randomized, double-blind clinical trial. Iranian journal of pharmaceutical research: IJPR 2012; 11(4): 1059.
28. Hadjibabaei M, Khoee S, Nematipoor E, Gholami K, Fatahian A, Jahangard Z. Comparison of efficacy and tolerability of different brands of amiodipine in patients with mild to moderate hypertension. Journal of Pharmaceutical Care 2015; 1(2): 41-4.
29. Namazi M, Yousefi Z, Shirazi M, Shaghkholeslami M, Vakili H, Mostamadi M, et al. Comparison of the clinical efficacy of three brands of warfarin. Indian journal of pharmacology 2004; 36(6): 360.
30. Manechnotesuwan K, Assawabhumi J, Rattanasangloet K, Suthamsmai T, Pipopsuthipaboos S, Udompunturak S. Comparison between the effects of generic and original salmeterol/fluticasone combination (SFC) treatment on airway inflammation in stable asthmatic patients. Journal of the Medical Association of Thailand= Chotmaihet thangphaet 2014; 97: S91-100.
31. Celik M, Tuncer A, Soyer OU, Sackesen C, Tanju Besler H, Kalayci O. Oxidative stress in the airways of children with asthma and allergic rhinitis. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 2012; 23(6): 556-61.
32. Caffarelli C, Calcinai E, Rinaldi L, Povesi Dascola C, Terracciano L, Corradi M. Hydrogen peroxide in exhaled breath condensate in asthmatic children during acute exacerbation and after treatment. Respiration; international review of thoracic diseases 2012; 84(4): 291-8.

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