Efficacy and Safety of Inhalex® Forte Versus Original Product in Asthmatic Adults: A Comparative Study

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Abstract

Objectives: To compare the efficacy of Inhalex® Forte and Berodual® Forte in stable bronchial asthmatic patients, after a methacholine–induced bronchoconstriction in terms of forced expiratory volume in one second (FEV₁) reversal within 90 minutes and adverse reactions.

Study design: randomized double-blind cross-over study

Methods: The study was conducted at the Asthma Clinic, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Khon Kaen. Inclusion criteria were participants aged from 18 to 60 years old who had stable asthmatic symptoms, FEV₁ more than 70% of the predicted normal value and had a positive methacholine provocation test. Exclusion criteria were patients with respiratory tract infection within six weeks, or asthma exacerbations within four weeks or had underlying diseases. Fifty participants completed the study and received a methacholine test and were randomly assigned to receive either one nebule of Inhalex® Forte or Berodual® Forte via micronebulizer. FEV₁ was measured at intervals until 90 minutes and reported as area under the curves (AUC) of FEV₁. One week apart within two hours of the previous time the participants were allocated to another medication. Participants, research assistants, assessors and data analyzers were blinded to the drug allocation. Oxygen saturation, blood pressure, pulse rate and any occurring adverse effects were monitored.

Results: There were 44 female (88%) and six male (12%) participants. Twenty-four patients had a history of allergic rhinitis. Average baseline FEV₁ was 2.5 ± 0.5 L. Percentage of FEV₁ of predicted normal value was 86.3 ± 10. Median difference of the area under the curve between the two study drugs was 0.36 which was not significantly different (P = 0.86, 95% CI -3.83, 4.94). No patients experienced any tachycardia or hypertension during the tests and no adverse effects occurred during the study.

Conclusion: The efficacy of Inhalex® Forte is comparable to Berodual® Forte, and no adverse events occurred in the administration of this drug.
Introduction

The tone of bronchial muscle depends on the balance between the activity of the parasympathetic and sympathetic divisions of the autonomic nervous system. It is possible to produce bronchodilatation either by stimulating the sympathetic pathway with sympathomimetic agents such as a short-acting $\beta_2$-agonist or inhibiting the action of the parasympathetic system using anti-cholinergic agents such as ipratropium bromide.

National and international guidelines for the treatment of acute severe asthma recommend the inhalation of short-acting $\beta_2$-agonists as first-line therapy due to its rapid onset and potent bronchodilatation. Addition of anticholinergic appears to improve lung function and reduce asthma admission. Although it has a slower onset of action but it has prolonged duration of action. The combination of these two medications not only maximizes bronchodilator effect but also minimizes unwanted side effects.

Berodual® Forte is an original combination of a bronchodilator, short-acting $\beta_2$-agonist (fenoterol hydrobromide) and an anticholinergic agent, ipratropium bromide, in one unit. This medication is very beneficial for the acute treatment and prevention of symptoms in chronic obstructive airway disorders with reversible bronchospasm such as bronchial asthma and chronic bronchitis with or without emphysema. Inhalex® Forte is also a combination between fenoterol hydrobromide and ipratropium bromide prepared by a Thai pharmaceutical manufacturer containing the same concentration of active ingredients as the original product. Previously there was no data available comparing the efficacy and adverse reactions between these two preparations. Therefore this study aims to compare between the original product, Berodual® Forte and Inhalex® Forte in terms of efficacy and safety in bronchial asthmatic adults.

Material and methods

Study design

This study was designed as a randomized double-blind cross-over study. To compare the efficacy of Inhalex® Forte and Berodual® Forte in stable bronchial asthmatic patients, after a methacholine-induced bronchoconstriction in terms of forced expiratory volume in one second ($\text{FEV}_1$) reversal within 90 minutes and adverse reactions.

Subjects

Subjects were recruited from the Asthma clinic, Srinagarind hospital, Faculty of Medicine, Khon Kaen University, Khon Kaen. Asthmatic adults age range from 18 to 60 years old were eligible for enrollment if they met all three inclusion criteria i.e. had stable asthmatic symptoms with no exacerbation and no change in medication within four weeks prior to the trial, had an initial forced expiratory volume in one second ($\text{FEV}_1$) more than 70% of the predicted normal value and had a positive methacholine provocation test. Patients will be excluded if they have either one of the following characteristics, presence of respiratory tract infection within six weeks prior to enrollment, presence of asthma exacerbations within four weeks prior to enrollment or are pregnant or lactating women. Excluded also were patients with a history of cigarette smoking more than ten pack-years or have hypersensitivity to $\beta$-adrenergic or anti-cholinergic. Further exclusion criteria were presence of underlying diseases which may affect the outcomes of interest including bronchopulmonary dysplasia or chronic lung disease, heart diseases with or without congestive heart failure, gastroesophageal reflux requiring medical treatment, receiving systemic corticosteroids in the past four weeks, receiving short-acting bronchodilator within six hours before methacholine or receiving long-acting bronchodilators within 24 hours before the methacholine challenge test. Discontinuation criteria in enrolled
subjects were any intolerance due to side effects or withdrawal by the patient.

**Randomization and study procedure**

Eligible stable asthmatic adults received the methacholine provocative test administered by a hand-held nebulizer. The starting dose of methacholine was 0.044 mmol and was increased with a double dose every one minute until the $FEV_1$ fell by at least 20% or the total dose of methacholine was 12.5 mmol (a positive methacholine provocation test). Then the patients were randomly allocated to receive either one nebul of Inhalex® Forte or Berodual® Forte driven by micronebulizer with oxygen 5 liters per minute. $FEV_1$ was measured at 0, 10, 15, 30, 60 and 90 minutes after the administration of the study drug. One week apart within two hours of the previous time the participants were allocated to another medication either Inhalex® Forte or Berodual® Forte. Both medications were prepared by a study nurse as a solution in inhalation form. Since they are identical in appearance, colour and odor. Participants, research assistants, physicians and the data analysts were blinded to the intervention.

Simple randomization was performed by computer-generated process and the codes of the allocation were concealed in sealed opaque envelopes while the name of the drugs were kept at the Clinical Research Center, Faculty of Medicine, Khon Kaen University. During all procedures, the participants in both groups were closely monitored for the oxygen saturation ($SpO_2$), blood pressure and heart rate. If $SpO_2$ dropped to less than 92%, oxygen therapy will be supplemented and in case of adverse events, physicians will take action.

**Statistical analyses**

A pilot study was performed in two patients administered with Berodual Forte® and revealed the mean of AUC during 60 minutes to be 26.26 Litre-hour while the standard deviation was 4.97. The AUC of subjects administered by Inhalex® Forte is assumed to be within 10% of those administered by Berodual® Forte.

Using one-sided test on data from a two-period crossover design, sample size of 50 participants in the Berodual® Forte group and 50 in the Inhalex® Forte group will achieve 90% power at a 5% significance level when the reference mean (AUC) is 26.26, the treatment mean is 28.8, the standard deviation is 4.97 and the range of the difference between these means that still results in the conclusion of equivalence is not less than 10% of the Berodual® Forte group mean with the dropout rate of 5%.

Baseline characteristics of the participants were summarized using descriptive statistics and presented in percentage, mean and standard deviation. The primary outcome analysis was based on intention-to-treat principle. $FEV_1$ during 90 minutes after each study drug intervention was calculated into area under the curve (AUC) and was compared using Wilcoxon signed rank test. The secondary outcomes were analyzed to compare the adverse events of the two groups during 90 minutes after intervention using McNemar Chi square test.
Ethical consideration

This study was approved by the Ethics Committee of Khon Kaen University for Human research. All patients participated voluntarily and provided informed consent. All information regarding the identification of participants was considered confidential and could be assessed by authorized investigators only. All the interventions are standard tests used for bronchial asthmatic patients. Any adverse events during interventions were closely observed and the study room was equipped with a full standard resuscitation set.

Results

All subjects who entered the trial (n=50) completed the study. There were 44 female (88%) and six male (12%) participants. Mean age 44 years. Twenty-four patients had a history of allergic rhinitis. All subjects stopped using any short-acting bronchodilator within six hours before methacholine or long-acting bronchodilators within 24 hours before the methacholine challenge test. Table 1 shows the baseline data of the subjects.

<table>
<thead>
<tr>
<th>Characteristic (n=50)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44 ± 9.6</td>
</tr>
<tr>
<td>Sex F/M</td>
<td>44/8</td>
</tr>
<tr>
<td>FEV₁ L</td>
<td>2.5 ± 0.5 (1.6-4.4)</td>
</tr>
<tr>
<td>FEV₁ % Pred</td>
<td>86.3 ± 10 (72-116)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD (range). F: female; M: male; FEV₁: forced expiratory volume in one second

L: Liter; Pred: predicted

Figure 1. Study flow diagram.
The geometric mean of the methacholine dose that was given until the FEV$_1$ fell by at least 20% (PD20) in A group (Inhalex® Forte) and was 0.67±1.24 mmol (95% CI 0.31, 1.02), and in B group (Berodual® Forte) was 0.68 ±1.05 mmol (95% CI 0.38, 0.98). There was no significant difference of the required dosage among participants in the two groups (P = 0.91).

Median difference of the area under the curve between the two study drugs was 0.36 which was not significantly different (P = 0.86, 95% CI -3.83, 4.94) as in Figure 2. No patients experienced any tachycardia or hypertension during the tests. No adverse effects occurred during the study, one subject had diarrhea at the second test which is not related to the administration of the study drug.

**Figure 2.** Mean area under the curves of FEV$_1$ within 90 minutes after methacholine challenge test and inhalation of Inhalex® Forte and Berodual® Forte.

A - - - Inhalex® Forte
B __ Berodual® Forte

**Discussion**

The combined drug preparation of a bronchodilator, short-acting β$_2$-agonist (fenoterol hydrobromide) and an anticholinergic agent, ipratropium bromide is very beneficial for the acute treatment and prevention of symptoms in chronic obstructive airway disorders with reversible bronchospasm such as bronchial asthma and chronic bronchitis with or without emphysema. In addition to the reversal of bronchoconstriction, the effect can persist until 8 hours and was suggested as an alternative...
to a monotherapy in chronic obstructive pulmonary disease.

This study compared the efficacy and adverse reactions between the original product Berodual® Forte and Inhalex® Forte. The study showed that there was no difference in reversing the bronchoconstriction induced by methacholine provocation test. The baseline characteristics among the asthmatic patients were similar including the dose of methacholine used in the provocation test, though there was a predominance of female patients. No patients experienced any adverse symptoms or events. Thus this new preparation is effective and safe to be used in this group of patients. The limitation of this study was that due to the feasibility we did not evaluate the effect on FEV₁ in the intermediate period (8 hours). Patients with chronic bronchitis with or without emphysema were not included; therefore the effect in this group of patients hasn’t been tested and maybe useful for future studies.

Conclusion

The efficacy of Inhalex® Forte is comparable to Berodual® Forte, and no adverse events occurred in the administration of this drug.

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Research Grant: Silom Medical Co., Ltd., Thailand

References


บทคัดย่อ: วัชรา บุญสวัสดิ์, อุไรวรรณ แซ่อุ่ย, สงวนศักดิ์ ธนาวิรัตนานิจ. การศึกษาเปรียบเทียบประสิทธิภาพและความปลอดภัยของยาอินฮาเล็กซ์ ฟอร์ทกับยาต้นแบบในผู้ป่วยผู้ใหญ่ที่เป็นโรคหอบหืด. วารสารวัณโรค โรคทรวงอกและเวชภัณฑ์กุศล 2557; 35: 45-51.

วัตถุประสงค์: เพื่อเปรียบเทียบประสิทธิภาพของยาอินฮาเล็กซ์ ฟอร์ทและ บีโรดูอัล ฟอร์ท ในผู้ป่วย stable bronchial asthma หลังจากได้รับการกระตุ้นการหดตัวของหลอดลมด้วย methacholine โดยวัดผลการเปลี่ยนแปลงของ forced expiratory volume in one second (FEV₁) ภายใน 90 นาที และอาการไม่พึงประสงค์จากการใช้ยา

รูปแบบการศึกษา: เป็นการศึกษาแบบสุ่มที่มีการปิดทับทางแบบไขว้.

ผลลัพธ์: มีผู้เข้าร่วมการศึกษาเป็นหญิง 44 คน (ร้อยละ 88) และเป็นชาย 6 คน (ร้อยละ 12). ผู้ป่วย 24 คนมีประวัติโรคจมูกอักเสบจากภูมิแพ้ ค่าเฉลี่ยเริ่มต้นของ FEV₁ คือ 2.5 ± 0.5 ลิตร เบอร์ซีดที่ FEV₁ จากค่าปกติที่ค่านอนได้คือ 86.3 ± 10 ลิตร ค่าความแตกต่างของค่ากลับของพื้นที่ได้รับผลระหว่างอายุ 2 ชนิดคือ 0.36 ซึ่งไม่แตกต่างกันอย่างมีนัยสำคัญ (P=0.86, 95 % CI -3.83, 4.94). ไม่มีผู้ป่วยคนใด มีภาวะหัวใจเต้นเร็วมีผลต่อการทำงานของกล้ามเนื้อการสูบและไม่มีอาการไม่พึงประสงค์จากการใช้ยาเกิดขึ้นระหว่างการศึกษา.

สรุปผลการศึกษา: ประสิทธิภาพของยาอินฮาเล็กซ์ ฟอร์ทเท่าเทียมกับ บีโรดูอัล ฟอร์ท และไม่มีอาการไม่พึงประสงค์จากการใช้ยาเกิดขึ้นขณะได้รับยานี้.