Effects of Budesonide and Fluticasone Propionate in Pediatric Asthma Patients

Lin-Yu Kuo¹, Chih-Hsing Hung¹,²,³, Hsing-I Tseng¹, Jiunn-Ren Wu¹,⁴, Yuh-Jyh Jong¹,²,³, Yu-Te Chu¹*

¹Department of Pediatrics, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan
²Department of Pediatrics, Faculty of Pediatrics, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
³Graduate Institute of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
⁴Department of Pediatrics, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung, Taiwan

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fluticasone

Background: Cytokines and chemokines play important roles in asthma. However, little information exists on the effects of inhaled corticosteroids on cytokine and chemokine plasma levels in childhood asthma. We compared the pharmaceutical effects of two inhaled corticosteroids used in pediatric patients with mild-to-moderate asthma, budesonide and fluticasone propionate.

Methods: Pediatric patients aged 5–18 years old were enrolled in this randomized, open-label, observer-blinded study and received 3 months of treatment with either inhaled budesonide (200 µg/puff) or fluticasone propionate (250 µg/puff), at two puffs per day. Peak expiratory flow (PEF), exhaled nitric oxide, Asthma Control Test (ACT), plasma levels of tumor necrosis factor-α, thymus and activation-regulated chemokine, and interferon-inducible protein 10 were measured before treatment and monthly for 3 months after treatment.

Results: There were six patients in the budesonide group, and eight in the fluticasone group. After 3 months, both groups showed improved PEF. In the first month, PEF improved more in the budesonide group than in the fluticasone group, though the difference was not significant. After treatment, ACT scores in both groups were well controlled, except for one patient in the fluticasone group. The fluticasone group had a more significant reduction in exhaled nitric oxide than the budesonide group in the first month.

Conclusion: Improvements in lung function were more rapid in the budesonide group than the fluticasone group. However, patients in the fluticasone group had better anti-inflammatory responses than those in the budesonide group. We conclude that each inhaled corticosteroids have its own clinical and laboratory effects.

*Corresponding author. Department of Pediatrics, Kaohsiung Medical University Hospital, 100 Tz-You 1st Road, Kaohsiung 807, Taiwan.
E-mail: yutechu@gmail.com

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1. Introduction

Asthma is a chronic inflammatory disorder characterized by airway hyperresponsiveness, airway inflammation, and reversible airway obstruction. Tumor necrosis factor-α (TNF-α) functions as a pro-inflammatory cytokine that leads to the recruitment of neutrophils and eosinophils in asthma. Elevated TNF-α levels have been detected in sputum, bronchoalveolar lavage, and biopsy samples from asthmatic patients. In addition to cytokines, chemokines also play an important role in asthma. Interferon-inducible protein 10 (IP-10) also known as chemokine (C-X-C motif) ligand 10, is a Th1-related chemokine that plays an important and influential role in human allergic pulmonary reactions. Infiltration of the airways by Th2 lymphocytes is also a well-recognized feature of bronchial asthma. Thymus and activation-regulated chemokine (TARC) is a Th2 chemokine involved in the recruitment of CC chemokine receptor 4-bearing Th2 cells during allergen-challenged inflammation.

Asthma Control Test (ACT) scores have been clinically validated and are as sensitive as the pulmonary function tests, which is the gold standard for monitoring asthma control. The ACT asks asthmatic patients to recall their asthma symptoms during the previous 4 weeks. Recent studies have shown that lower ACT scores are associated with poorer asthma outcomes, such as more emergency room visits and hospitalizations. Thus, ACT has become a useful tool in asthma management.

As recommended by the Global Initiative on Asthma (GINA) guidelines, a consensus protocol currently exists for anti-inflammatory treatment of childhood asthma. Inhaled glucocorticosteroids (ICS), the most effective medication available, can reduce asthma symptoms and exacerbations, and bronchial hyperresponsiveness; it can also improve lung function. The therapeutic effects of ICS are related to their ability to modulate immune responses by altering the number of inflammatory cells and the expression of inflammatory mediators.

Budesonide and fluticasone propionate are two inhaled glucocorticoid drugs that have been used in children with mild-to-moderate asthma for a long time. Plasma levels of TNF-α (pro-inflammatory), IP-10 (Th1) and TARC (Th2) increase during asthma exacerbations, and are thus used as inflammatory markers of asthma exacerbations in children. In the current study, we investigated the clinical responses that result from budesonide and fluticasone propionate treatment respectively, by comparing ACT results, exhaled nitric oxide (eNO) and peak expiratory flow (PEF). We also examined which agent produced a better anti-inflammatory effect in asthma patients by evaluating changes in plasma levels of TNF-α, TARC and IP-10.

2. Materials and Methods

2.1. Patients

The Institutional Review Board of Kaohsiung Medical University Hospital approved the study protocol (KMUH-IRB-960141). The study was conducted as an observer-blinded, randomized design, open-label cohort study. Pediatric patients aged 5–18 years old and who had suffered from asthma attacks between September 2007 and June 2008, were recruited to the study. The children enrolled in this study were classified as having mild-to-moderate asthma, as defined by the GINA guidelines. Participants who have had acute febrile respiratory tract infections or received previous cortico-steroid treatment were excluded; those hospitalized were also excluded from the study. A total of 20 children were randomly assigned to receive 3 months of treatment with either fluticasone or budesonide in the outpatient clinic of our hospital. Informed consent was obtained from parents.

The clinical severity of asthma was defined as mildly persistent if symptoms were observed more than once per week; PEF was >80% of the predicted or personal best, and PEF variability was between 20% and 30%. The severity was defined as moderately persistent if symptoms occurred daily, PEF was between 60% and 80% of predicted or personal best, and PEF variability was >30%.

The childhood ACT is a seven-item assessment tool designed for children 4–11 years of age and is completed by the child and parent/caregiver. Scores range from 0 to 27. For asthma patients aged 12 years and older, the ACT is a five-item patient-completed questionnaire that compares well with asthma specialists’ global assessment of asthma control; the measure is also responsive to changes in asthma control over time. Scores range from 0 to 25. In our study, asthma was defined as not controlled if the score was ≤19, well controlled if the score was ≥20. Those who were febrile or received ICS were excluded. After parental informed consent was obtained, patients were followed for 3 consecutive months.

2.2. Study design

Patients were divided into two randomized groups. One group was given 200 μg/puff budesonide (Obucort Swinghaler, Taiwan Otsuka Pharmaceutical Co. Ltd., Taipei, Taiwan). The other group was given
250 μg/puff fluticasone propionate (Flixotide Accuhaler, GlaxoSmithKline, Ware, UK). Both treatments were administered twice per day. The dosages of the two inhaled corticosteroids were equivalent to therapies for mild-to-moderate asthma, based on the GINA guidelines. PEF was measured using a peak flow meter (Asthco Co., Port Washington, NY, USA), and eNO concentrations were measured using the single-breath technique with a chemiluminescence analyzer (CLD 88 Exhalizer; Eco Medics AG, Dürnten, Switzerland). Plasma samples were stored at −70°C immediately after sampling. Plasma cytokine and chemokine levels were measured using a commercially available enzyme-linked immunosorbent assay systems (R&D Systems, Minneapolis, MN, USA). An independent observer unaware of the grouping assignment followed the patients and recorded the PEF and ACT results. ACT scores, PEF, eNO, and plasma levels of TNF-α, TARC, and IP-10 were measured both before (at the beginning of study) and after treatment (after 1, 2 and 3 months).

2.3. Statistical analysis

SPSS version 12.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Plasma levels of TNF-α, TARC, and IP-10 were analyzed using the Wilcoxon signed-rank test. Differences were considered significant when \( p < 0.05 \).

3. Results

3.1. Demographic data of subjects

Twenty patients were initially enrolled and 14 completed the study. One patient was excluded due to active tuberculosis; five other patients were excluded due to lack of follow-up after the first month. The age distributions, body weights, and heights did not differ significantly between the two groups (Table 1). Patients who were eligible for the study were randomly assigned to receive either inhaled fluticasone propionate or budesonide for 3 months. Eight patients received fluticasone propionate (male:female, 6:2), and the other six patients received budesonide (male:female, 5:1). The age distributions did not differ significantly between the two groups (Table 1).

3.2. Changes in eNO level after treatment

As shown in Figure 1A, eNO levels were significantly reduced after 1 month of fluticasone propionate treatment (47.95 ± 11.67 ppb vs. 20.74 ± 3.87 parts per billion (ppb), \( p = 0.006 \), and after 2 months (47.95 ± 11.67 vs. 23.26 ± 12.68 ppb, \( p = 0.009 \)). However, 1 month of treatment with budesonide significantly increased eNO levels (39.28 ± 6.20 vs. 62.03 ± 12.08 ppb, \( p = 0.014 \)), but after 3 months, eNO levels returned to a level similar to the pretreatment level (39.28 ± 6.20 vs. 38.38 ± 17.66 ppb, \( p = 0.447 \)).

3.3. Predicted PEF during the treatment course

A significant increase in predicted PEF occurred following 2 months of fluticasone propionate treatment (89.19 ± 9.58% vs. 97.65 ± 6.57% , \( p = 0.047 \), and after 3 months (89.19 ± 9.58% vs. 101.07 ± 8.02%, \( p = 0.01 \)). Budesonide also significantly increased predicted PEF after the first (82.24 ± 6.28% vs. 102.86 ± 1.25%, \( p = 0.01 \)), second (82.24 ± 6.28% vs. 105.26 ± 5.89%, \( p = 0.04 \)), and third months (82.24 ± 6.28% vs. 107.94 ± 5.64%, \( p = 0.02 \)). The change in PEF after the first month was greater in the budesonide group, though the difference between the two groups was not significant.

3.4. Changes in ACT scores after treatment

Patients were asked to complete the ACT test during the treatment period. The ACT scores indicated good asthma control in both treatment groups, except for one patient in the fluticasone propionate group (Table 2).

3.5. Change in plasma TNF-α, TARC and IP-10 concentrations after treatment

Plasma TNF-α, IP-10 and TARC concentrations all increased in the first month in the budesonide group; however, the levels all declined to their baseline values in the third month (Figures 2A, 2B, and 2C). The fluticasone propionate group showed slight variations in plasma TNF-α, TARC and IP-10 levels during the course of treatment.

TNF-α levels in the fluticasone propionate group remained low throughout the entire period, while TNF-α levels in the budesonide group increased in the first month and then gradually declined to the baseline value. The concentrations of IP-10 and

### Table 1 Demographic data

<table>
<thead>
<tr>
<th></th>
<th>Budesonide</th>
<th>Fluticasone propionate</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:female</td>
<td>5:1</td>
<td>6:2</td>
<td>0.71</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>10.2 ± 3.5</td>
<td>10.8 ± 4.0</td>
<td>0.77</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>135.0 ± 14.5</td>
<td>138.9 ± 23.2</td>
<td>0.71</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>36.7 ± 9.6</td>
<td>47.1 ± 30.4</td>
<td>0.39</td>
</tr>
</tbody>
</table>
TARC in the budesonide group increased in the first month and then declined to their baseline values in the third month. Budesonide significantly increased plasma TARC concentrations after the first 2 months of treatment (149.35 ± 38.48 vs. 180.52 ± 28.42 ppb, p = 0.01). Plasma TARC concentrations showed slight variations in the fluticasone propionate group. The IP-10 level in the fluticasone propionate group was lower than that of the budesonide group during the course of treatment. However, there were no significant differences between the two groups in plasma TARC, IP-10 or TNF-α concentrations.

4. Discussion

The use of ICS to reduce chronic inflammation is a cornerstone treatment for asthma. ICS can reduce asthma symptoms and inhibit the activities of inflammatory cells, including eosinophils, T lymphocytes, mast cells, macrophages, dendritic cells and neutrophils. Budesonide and fluticasone propionate have been effectively used to prevent the development of asthma in high-risk children. In the present study, both groups showed improved PEF and well-controlled ACT scores, indicating that the two drugs could improve pulmonary function as well as clinical symptoms and signs.

PEF showed greater improvement in the budesonide group than in the fluticasone group. The clinical efficacy of ICS depends on the topical activity of the drug that reaches the lungs. The amount of drug delivered to the lungs depends on the inhalation technique, type of inhaler used, delivery of differently sized particles, and whether or not spacers are used. The Swinghaler is a high-delivery device with a low inspiratory flow that emits powder through a horizontal inhalation channel. The range of optimum inspiratory flow is widespread. Due to their different designs, the Swinghaler might be better than the Accuhaler in improving PEF.

Recent studies have shown that the bronchial epithelium in asthmatic patients expresses IP-10 and TARC, which have been implicated in the recruitment of Th1 and Th2 cells to inflammatory airways. TARC and IP-10 are useful inflammatory markers of asthma exacerbations in children. TNF-α is expressed in various cells in asthmatic airways, particularly in mast cells, and it plays a
key role in amplifying asthmatic inflammation.\textsuperscript{22}

In the present study, plasma TNF-α, IP-10 and TARC increased after 1 month of treatment in the budesonide group, but declined to their baseline values after 3 months of treatment. In contrast, the fluticasone propionate group showed slight variations in plasma TNF-α, TARC and IP-10 levels during the course of treatment. With respect to eNO, elevated eNO levels were observed in the budesonide group during the first and second months of treatment, and the eNO levels almost declined to the pretreatment level in the third month; eNO level showed a decrease after treatment in the fluticasone group.

Of note was that in the current study, the eNO level was higher in the budesonide group than in the fluticasone group. Levels of eNO have been shown to correlate predominantly with eosinophilic airway inflammation, and can be reduced by ICS therapy.\textsuperscript{23} Moreover, eNO levels fell significantly after treatment in the fluticasone propionate group. Significantly elevated eNO levels were observed in the budesonide group during the first month of treatment, although it fell almost to the pretreatment level in the third month. Fluticasone was shown to maintain TNF-α, IP-10 and TARC at constant levels, whereas budesonide led to elevated levels of TNF-α and TARC during treatment. Taken together, these observations suggest that fluticasone propionate had a greater anti-inflammatory effect than budesonide in our study. Factors such as nitrate-containing foods or allergic rhinitis can influence the concentration of eNO;\textsuperscript{24} these factors could potentially account for the observation that eNO levels were elevated in the budesonide group, despite clinical improvements.

Budesonide and fluticasone propionate are both ICS, but they demonstrated divergent effects in this study. The two kinds of ICS have close chemical and structural similarities. However, they use different pharmacokinetic and delivery device designs, which could lead to differences in their clinical effects. Potency, a measure of the microgram dose of a drug required to produce a standard response,
is greater for fluticasone propionate than for budesonide.\textsuperscript{25} In comparison to budesonide, fluticasone propionate also exhibits considerably greater glucocorticoid receptor-binding affinity,\textsuperscript{25} and has been demonstrated to have a longer lung retention time.\textsuperscript{26} Thus, these factors could account for the superior anti-inflammatory effect of fluticasone propionate compared with budesonide.

There were several limitations to the current study. Due to the frequent blood-sampling requirements, the total number of patients that completed this study was small because some patients refused to continue with the protocol. Also, PEF tests were difficult to perform in patients younger than 6 years old. Drug compliance also tends to be particularly variable in pediatric patients. Further limitations also includes confounding factors such as environmental effects or allergen avoidance, which could not be eliminated.

In conclusion, patients in the budesonide group had greater improvements in lung function, and clinical symptoms and signs than those in the fluticasone propionate group. Nevertheless, the fluticasone propionate group experienced a better anti-inflammatory response than the budesonide group. We conclude that the two different ICSs have divergent clinical and laboratory effects.

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