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Moderate Persistent Asthma Treated with Combined Budesonide-Formoterol Inhaler: A Case Report

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Abstract: ***Asthma is a chronic respiratory disease with increasing prevalence around the world.Asthma can affect the patient's quality of life in the long term, therefore therapy for asthma is very important. Patient's compliance is very crucial in asthma therapy. Combined Budesonide plus Formoterolin a single inhaler is an asthma therapy that may be used for both maintenance and reliever. This case report presents a case of 34-year-old male which was diagnosed with moderate persistent asthma and wasmanaged with inhaled budesonide plus formoterol. There was an increase of Asthma Control Test from 11 into 24 after one month therapy and there was no exacerbation. Unfortunately, the patient was not adhere to the treatment because he was already feeling healthy. There was no improvement from the spirometry test, possibly because short follow-up or lack of patient's compliance. Single inhaler is easier and more applicable to the patient compared to budesonide and formoterol via separate inhaler. This study showed that Combined Budesonide - Formoterol inhaler could be used as a therapy for moderate persistent asthma, but patient compliance is very important to determine the success of the therapy.***

Keywords: moderate persistent asthma, budesonide, formoterol, inhaler

1. Introduction

Asthma is a respiratory disease that affects many people in various parts of the world. The definition of asthma according to the Global Initiative for Asthma (GINA) is a heterogeneous disease characterized by chronic airway inflammation. It is definedby a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness, and coughing that vary over time and in intensity, along with limited expiratory airflow.[1]

Asthma prevalence varies around 1-18% in the world.[1] According to Centers for Disease Control and Prevention (CDC), there was 10 death per million of population caused by asthma in 2016. The mortality of asthma was decreased compared to year 2001, but the prevalence tends to increase every year. Most of the deaths in asthma are due to the delay in medical treatment when an asthma exacerbation recurs.[2]
Based on the etiology, asthma can be divided into atopic asthma and non-atopic asthma. Atopic asthma is caused by the patient's sensitivity to allergens, while non-atopic asthma is caused by other than allergens. In atopic asthma, the pathophysiology begins with exposure to allergens. In people who are allergic, Th2 cells will exceed Th1 cells. Th2 cells will increase the synthesis of IL-4 and IL-13 genes. The gene triggers B cells to produce IgE which will bind to mast cells. Once IgE reacts with antigen, mast cells will release mediators that cause airway obstruction due to airway smooth muscle constriction and eosinophilic airway inflammation. In non-atopic asthma, asthma occurs due to sympathetic nerve impairment, namely beta adrenergic blockade and alpha adrenergic hyperreactivity which causes bronchoconstriction.[3]

Asthma is a chronic disease that can affect the patient's quality of life in the long term, therefore therapy for asthma is very important. There are two types of medication for asthma, known as "relievers" and "controllers". Reliever medicine is intended to alleviate acute symptoms of asthma and only used in acute events, while controller is taken on a regular basis to prevent asma attacks.[4]The asthma inhaler that may be used for both maintenance and relief is Symbicort® which contains Inhaled Budesonide plus Formoterol in a single inhaler.

Randomized controlled trial (RCT) showed that in patients who were not totally controlled by glucocorticosteroids alone, budesonide/formoterol single inhaler therapy provides better asthma control than budesonide alone.[5] This report present a case of moderate persistent asthma treated with combined budesonide-formoterol inhaler.

2. Case Illustration

A 34 year male came to the Emergency Room with chief complaint of shortness of breath that has been getting worse since this morning. The shortness of breath limit patient activity, patient could only talk in phrases, and prefers sitting compared to lying position.The patient also had wet cough since yesterday. Patient did not complain of chest pain. There was no history of swelling in the lower extremities. Patient had history of asthma with symptoms that occurs daily, and last admission was two weeks ago in the other hospital. History of other systemic disease such as hypertension was denied. General examination revealed consciousness was compos mentis, blood pressure 140/90 mmHg, pulse 120 beats per minute, respiration 28 times per minute, axillary temperature 36.5^{0}C, and oxygen saturation was 98% in room air. Physical examination revealed symmetric chest movement, chest retraction, and wheezing on all lung's area during auscultation. The cardiac examination showed regular rhythm with no murmur nor gallop. The remaining systemic examination was within normal limit.

Complete blood test of the patient shows: Leukocytes 17.88 x 10^3/µL; Hemoglobin 15.1 g/dL; Hematocrit 43.4%; Platelets 263 x 10^3/µL; Neutrophyl90.2%; Lymphocyte 4.1%. Renal function test, liver function test, serum electrolyte, and blood glucose were within normal limit. Antigen SARS CoV 2 was non-reactive. Chest X-ray revealed bronchitis (Fig 1.)

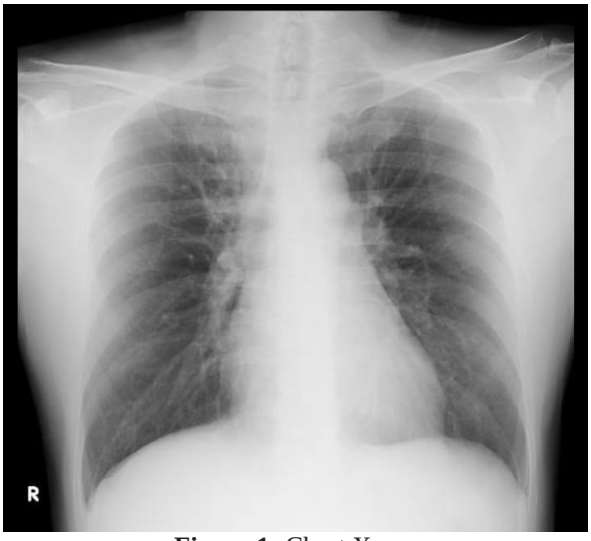

Figure 1: Chest X-ray

The patient was diagnosed with moderate asthma exacerbation on moderate persistent asthma. Initial therapy addressed to this patient on Emergency Room was Combivent® (ipratropium bromide + salbutamol) and Flixotide™ (fluticasone propionate) nebulizer twice. The dyspnea was persistent after twice nebulizer, therefore the patient was given O_2 6 liters per minute using face mask, intravenous hydrocortisone 100 mg, and Ventolin™ + Pulmicort® (budesonide) nebulizer. There was still no improvement therefore the patient was admitted to hospital with O_2 3 liters per minute via nasal can use; bolus aminophylline 120 mg + normal saline 5 ml run out in 20 minutes and if heart rate was less than 120 bpm, can be continued aminophylline 360 mg in normal saline 500 ml run out in 12 hours; cefoperazone sulbactam 1 gram twice a day; ambroxol 30 mg thrice a day; N-acetyl-cysteine (NAC) 200 mg twice a day; hydrocortisone 100 mg twice a day; and Combivent® + Pulmicort™ nebulizer every 8 hours.

On the next day, the shortness of breath had been subsided. The patient was discharged after three day of admission. The patient undergo spirometry test with spirometer (Datospir Touch Sibelmed) which have been routinely calibrated and the patient's maneuvers was already correct. The initial spirometry results showed that FEV1%was 64% and VC was 79%. The initial score asthma control test was 11. The patient was given Symbicort (budesonide-formoterol) as reliever and maintenace therapy. The FEV1% wasincreaseto 82% after the administration of Symbicort.

After one month, the patient came for follow up. There was no exacerbation. The asthma control test increased from 11 into 24. Unfortunately, the patient didn't adhere to the therapy due to already feeling healthy.The FEV1% was 57% and VC was 80%.

3. Discussion

The patient in this case came to ER with complaints of shortness of breath which limit patient activity, patient could only talk in phrases, and prefers sitting compared to lying position.Patient had history of asthma with symptoms that occurs daily. Physical examination revealed increased respiration rate into 28 times per minutes, chest wall retraction, and wheezing on auscultation. Therefore, the patient was diagnosed with moderate asthma exacerbation on moderate persistent asthma.[1]

During admission, the patient was given salbutamol + ipratropium bromide and budesonide nebulizer, aminophylline, systemic hydrocortisone, ambroxol, NAC, and cefoperazone.Salbutamol is a short acting β-2 agonist, ipratropium bromide is an anticholinergic, budesonide and hydrocortisone are corticosteroid, NAC and abroxol are mucolytics, and cefoperazone is an antibiotics. In asthmatic patient, airway smooth muscle constriction can be treated with short-acting and long-acting β-2 agonists, eosinophilic airway inflammation is treated with inhaled corticosteroids,whilechronic bacterial infection is treated with antibiotics. The patient had high level of leukocytes and neutrophylpercentage, therefore antibiotic was given. Mucolytic is used to alleviate cough symptoms.[3]

Combined budesonide-formoterol inhaler was given to the patient for outpatient therapy. Budesonide is a corticosteroid while formoterol is a long-acting β2-agonist. Mechanism of action of budesonide is reducing inflammation while formoterol is by causing bronchodilatation.Budesonide will binds to glucocorticoid receptors (GR) in bronchial cytoplasm, and allows the translocation of budesonide-GR complex in the bronchi nucleus, which binds to gene encoding enzyme histone deacetylase 2 (HDCA2) and histone acetyltransferase (HAT). This will prevents the production of inflammatory genes such as ILs and TNF that might cause bronchoconstriction[6]

Formoterol increased the expression of inflammatory genes in human bronchial epithelial cells, while the glucocorticoid budesonide decreased many of these alterations. This is the reason why combining a LABA with an inhaled corticosteroid may improve clinical outcome in asthma.[7]

A 12-week, double blind, randomized controlled trial (RCT) involving 362 asthmatic adult concluded that single inhaler budesonide-formoterol two inhalations twice a day is better than budesonide alone in improvement of lung function and symptoms score.[5] This was differenttoour study probably because short term follow-uptime in our study whichisonly in 4 week. There is also no protocol to control patient's compliance in our study.

Another 6-months double blind RCT in 3335 symptomatic adults and adolescents showed that Budesonide-formoterol single inhaler for maintenance and relief reduces asthma exacerbations and maintains similar daily asthma control at a lower overall drug load compared with fixed-dose salmeterol-fluticasone (Rate reduction 0.61; $p < 0.001$; 95% CI 0.49–0.76) and vs fixed-dose budesonide/formoterol + terbutaline (0.72; $p = 0.0048$; 95% CI 0.57–0.90).[8] A 12

months randomised open label in 2,143adults and adolescents showed thatBudesonide-formoterol single inhaler for maintenance and relief prolonged the time to first severe exacerbation versus salmeterol/fluticasone (risk reduction 25%).[9]

A cross-sectional multicenter study among 1483 patients in 27 centers showed that asthma of patients and was either controlled or partly controlled with budesonide-formoterol in 94.1% patients (95% CI: 92.8%-95.3%) according to GINA criteria. According to ACT score, asthmawas either completely or well controlled in 83.3% (95% CI: 81.4%-85.2%) of patients.[10]

Beside in moderate and severe asthma, combined budesonide-formoterol inhaler also shows to be superior than terbutaline in mild asthma. In a 52-week, double-blind, randomized controlled trial comparing budesonide-formoterol as needed to terbutaline as-needed in patients with mild asthma, budesonide-formoterol was better than terbutaline in percentage of week with well controlled asthma (34.4% vs. 31.1% weeks; OR 1.14; 95% CI 1.00 - 1.30; p=0.046). The annual rate of severe exacerbations was 0.20 with terbutaline, 0.07 with budesonide-formoterol, and 0.09 with budesonide maintenance therapy.[11]

Budesonide-Formoterol in a single inhaler has several advantages such aseasy to carry, easy to use, and more comfortable for the patients compare to budesonide plus formoterol via separate inhalers, thereby possibly increasing patient compliance.[8]

4. Conclusion

Combined Budesonide - Formoterol inhaler as a maintenance and reliever therapy for moderate persistent asthma in our patient showed improvements in ACT score and spirometry results.

Unfortunately this patient didn't comply to therapy which resulted in abnormal spirometry result after one months follow-up. Good patient's compliance is needed for management of asthma.

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