A RANDOMIZED CONTROLLED TRIAL ON THE USE OF BUDESONIDE/FORMOTEROL (SYMBICORT®) AS AN ALTERNATIVE RELIEVER MEDICATION FOR MILD TO MODERATE ASTHMATIC ATTACK IN ADULT PATIENTS IN EMERGENCY DEPARTMENT, HOSPITAL UNIVERSITI SAINS MALAYSIA

By:

DR HAMIZAH BINTI KAMARUDIN

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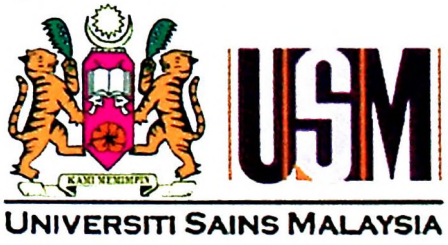

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LIST OF ABBREVIATIONS

ACT	Asthma Control Test
α-agonist	Alfa agonist
β-agonist	Beta agonist
COPD	Chronic obstructive pulmonary disease
ED	Emergency department
FENO	Fraction Exhaled Nitric Oxide
GINA	Global Initiative For Asthma
ICS	Inhaled corticosteroid
LABA	Long Acting β2- agonist
MDI	Metered dose inhaler
PEFR	Peak Expiratory Flow Rate
ppb	Parts per billion
RR	Respiratory Rate
SABA	Short Acting β2- agonist
SPO2	Oxygen saturation
SMART	Symbicort Maintenance and Reliever Therapy
VAS	Visual Analog Score

ABSTRAK

KAJIAN MENGENAI KEBERKESANAN BUDESONIDE/FORMOTEROL (SYMBICORT) TUBUHALER SEBAGAI RAWATAN ALTERNATIF UNTUK SERANGAN AKUT RINGAN DAN SEDERHANA TERUK PESAKIT ASMA DI JABATAN KECEMASAN, HUSM

PENGENALAN

Nebulised Salbutamol merupakan rawatan konvensional yang biasa diberikan untuk serangan akut asma samada di klinik atau di jabatan kecemasan. Manakala, Symbicort turbuhaler merupakan gabungan Formoterol (long acting β2-agonist) dan Budesonide (steroid). Salbutamol dan Formoterol adalah merupakan ubat yang bertindak sebagai β2-agonist yang memberikan kesan pembukaan salur pernafasan, cuma jangka masa tindakan Salbutamol adalah lebih pendek berbanding dengan Formoterol. Budesonide pula merupakan sejenis steroid yang berfungsi untuk mengawal inflamasi yang sering berlaku dalam serangan akut asma.

Kajian ini dijalankan adalah untuk melihat keberkesanan Symbicort turbuhaler yang merupakan gabungan steroid dan β2-agonist sebagai rawatan alternatif untuk serangan akut ringan dan sederhana teruk pesakit asma dan juga untuk melihat tahap kawalan dan penerimaan pesakit asma dalam menggunakan Symbicort turbuhaler sebagai terapi kelegaan dan kawalan (SMART).

OBJEKTIF

Objektif umum kajian ini adalah:

1) Mengkaji keberkesanan Symbicort terapi sebagai rawatan alternatif untuk serangan akut ringan dan sederhana teruk pesakit asma

Spesifik objektif:

1) Untuk megetahui tahap kawalan asma dikalangan pesakit asma dewasa yang hadir mendapatkan rawatan di HUSM dengan menggunakan skor Asthma Control Test (ACT)
2) Untuk menilai keberkesanan symbicort terapi sebagai rawatan alternatif untuk serangan akut ringan dan sederhana teruk pesakit asma dengan menggunakan kadar pernafasan, nilai oksigen dalam darah (SPO2) dan kadar hembusan nafas tertinggi (PEFR) sebagai penilaian objektif untuk menilai tahap keterukan serangan asma dan respon terhadap rawatan
3) Untuk menilai keberkesanan symbicort terapi sebagai rawatan alternatif untuk serangan akut ringan dan sederhana teruk pesakit asma dengan menggunakan Skala Visual Analog (VAS) dan Skala 5-point Likert untuk tahap kesukaran bernafas sebagai penilaian subjektif untuk menilai tahap keterukan serangan asma dan respon terhadap rawatan
4) Untuk mengetahui tahap penerimaan pesakit terhadap penggunaan Symbicort sebagai terapi kelegaan dan kawalan (SMART) dalam rawatan asma
5) Untuk mengetahui nilai hembusan nitric oksida pada pesakit asma dan kaitannya dengan kawalan asma

METODOLOGI

Satu kajian yang melibatkan penggunaan 2 jenis ubat (nebulizer Salbutamol dan Symbicort turbuhaler) telah dijalankan dari bulan Mac sehingga Ogos 2011 ke atas pesakit asma yang mengalami serangan akut ringan dan sederhana teruk yang hadir ke Jabatan Kecemasan Hospital Universiti Sains Malaysia. Pesakit yang memenuhi kriteria dan bersetuju menyertai kajian ini telah dipilih secara rawak untuk diberikan rawatan nebulizer salbutamol ataupun Symbicort turbuhaler. Bacaaan parameter objektif seperti kadar pernafasan, nilai oksigen dalam darah (SPO2), kadar hembusan nafas tertinggi (PEFR) termasuk ukuran hembusan nitrik oksida (FENO) serta parameter subjektif berdasarkan Skala Visual Analog (VAS) dan Skala 5-point Likert untuk tahap kesukaran bernafas sebelum dan selepas penggunaan ubat masing-masing direkodkan. Selain itu, borang kaji-selidik diberikan untuk menilai tahap kawalan asma dan tahap penerimaan pesakit terhadap peggunaan Symbicort turbuhaler dan terapi SMART (Symbicort Maintenance and Reliever Therapy).

Pesakit seterusnya diberikan temujanji selama sebulan untuk menilai semula tahap kawalan asma dan nilai bacaan FENO mereka. Perkaitan antara 2 ubat tersebut dan pembolehubah-pembolehubah dianalisa menggunakan program SPSS versi 18.0.

KEPUTUSAN

Seramai 32 orang pesakit asma yang memenuhi kriteria dan telah bersetuju menyertai kajian ini. Setelah dipilih secara rawak, 17 pesakit daripadanya dipilih untuk menerima rawatan nebulizer salbutamol dan selebihnya menerima rawatan symbicort. Hasil kajian mendapati kesan perubahan yang diperolehi oleh pesakit yang menerima rawatan symbicort dari segi kadar pernafasan (RR), nilai oksigen dalam darah (SPO2) dan kadar hembusan nafas tertinggi (PEFR) adalah signifikan (p=0.001 untuk RR, p=0.027 untuk SPO2 dan $p<0.001$ untuk PEFR) sebagaimana rawatan konvensional nebulizer salbutamol. Apabila dibandingkan purata perbezaan kesan perubahan-perubahan ini diantara kedua-dua kumpulan ini melalui ujian 'Independence t-test' didapati ia adalah tidak signifikan (p=0.687 untuk perubahan RR, p=0.350 untuk perubahan SPO2 dan p=0.507 untuk perubahan PEFR).

Dari segi parameter subjektif berdasarkan 'Visual Analog Scale' dan 5-point Likert scale' untuk tahap kesukaran bernafas, juga didapati tiada perubahan signifikan antara kedua-dua kumpulan rawatan ini (p=0.765 dan p=0.688).

Mengenai kawalan asma melalui "Asthma Control Test' (ACT), setelah menggunakan ujian Mc Nemar, didapati tiada perbezaan yang signifikan dalam kawalan asma bagi pesakit yang menerima rawatan terapi SMART dengan pesakit yang menggunakan MDI salbutamol dan MDI budesonide sebagai terapi kawalan (p=0.754). Terapi SMART juga didapati boleh diterimapakai dengan baik oleh kebanyakan pesakit melalui borang kaji selidik yang diberi.

KESIMPULAN

Hasil daripada kajian ini mendapati bahawa symbicort turbuhaler boleh digunakan sebagai rawatan alternatif bagi merawat serangan akut ringan dan sederhana teruk pesakit asma kerana terbukti tiada perbezaan yang signifikan bagi kesan perubahan dari segi parameter objektif (kadar pernafasan, nilai oksigen dan kadar hembusan nafas tertinggi) dan parameter subjektif (skala visual analog dan skala 5-point Likert untuk tahap kesukaran bernafas) yang didapati dengan rawatan nebulise salbutamol.

ABSTRACT

A RANDOMIZED CONTROLLED TRIAL ON THE USE OF BUDESONIDE/FORMOTEROL (SYMBICORT®) AS AN ALTERNATIVE RELIEVER MEDICATION FOR MILD TO MODERATE ASTHMATIC ATTACK IN ADULT PATIENTS IN EMERGENCY DEPARTMENT, HOSPITAL UNIVERSITI SAINS MALAYSIA

INTRODUCTION

Nebulized Salbutamol has been commonly used as the conventional reliever in the treatment of patients with acute exacerbations of asthma regardless of whether in outpatient clinic settings or in the emergency departments. On the other hand, Symbicort turbuhaler is a combination of Formoterol (long acting β2- agonist) and Budesonide (steroid).

Salbutamol and Formoterol are β2-agonist that acts as bronchodilators, but Salbutamol is a short acting β2-agonist, whereas Formoterol is a long acting β2-agonist. Budesonide is a steroid that plays a role as an anti-inflammatory agent that usually occur in acute asthma attack. This research is done to evaluate the effectiveness of Symbicort turbuhaler which is a combined long acting β2-agonist and steroid as an alternative reliever in mild to moderate acute axacerbation of bronchial asthma and to look at patient's acceptance regarding the use of Symbicort turbuhaler and the

feasibility in starting Symbicort maintanance and reliever therapy (SMART) in emergency department.

OBJECTIVES

General Objective

1) To evaluate the effectiveness of Symbicort therapy as an alternative reliever in treating mild to moderate acute exacerbation of bronchial asthma.

Specific Objectives

1) To evaluate control of asthma based on Asthma Control Test (ACT) among adult asthmatic patients that presented to emergency department HUSM.
2) To evaluate the effectiveness of Symbicort turbuhaler as an alternative treatment for mild to moderate asthma exacerbation by using respiratory rate, oxygen saturation and peak expiratory flow rate (PEFR) as objective assessment tools for the severity of asthmatic attack and patient's response to treatment.
3) To evaluate the effectiveness of symbicort turbuhaler as an alternative treatment for mild to moderate asthma exacerbation by using Visual Analog Score (VAS) and 5-point Likert Scale of breathlessness as subjective assessment tools for the severity of asthmatic attack and patient's response to treatment.
4) To understand patient's acceptance regarding the use of Symbicort turbuhaler as an acute asthma reliever and maintainance therapy (SMART).
5) To evaluate the fraction exhaled nitric oxide (FENO) level in asthmatic patient and its association with asthma control.

METHODOLOGY

A randomized controlled trial was done from March until August 2011 between nebulizer Salbutamol and Symbicort turbuhaler in adult patients with mild to moderate acute exacerbation of bronchial asthma who presented to Emergency Department HUSM. Patients who fulfilled the criteria and agreed to participate in this study were randomly assigned either nebulizer Salbutamol or Symbicort turbuhaler as the treatment. Objective and clinical parameters such as respiratory rate (RR), oxygen saturation (SPO2), peak expiratory flow rate (PEFR) and fraction of exhale nitric oxide (FENO) were recorded before and after treatment. Parameters were analyzed using SPSS version 18.0.

RESULTS

A total of 32 patients fulfilled the inclusion criteria and consented to participate in this study. After randomization, 17 patients were chosen to receive nebulized salbutamol and another 15 patients received symbicort turbuhaler. There were significant improvements in respiratory rate (RR), oxygen saturation (SPO2) and PEFR in patients received symbicort turbuhler (p=0.001, p=0.027 and p=*<0.001* respectively). This result is as significant as patients received nebulized salbutamol. When comparing the means difference between this two groups using 'Independence t-test', it showed that there were no significant difference in terms of changes in respiratory rate, SPO2 and PEFR (p=0.687, p=0.350 and p=0.507 respectively).

In terms of subjective parameters using 'Visual Analog Score' and '5-point Likert Scale' of breathlessness, it also showed that there were no significant difference in patients who received symbicort turbuhaler or nebulized salbutamol (p=0.765 and p=0.688 respectively).

Regarding asthma control based on Asthma Control Test (ACT) score, by using Mc Nemar test, there were no significant difference in asthma control in patients started on SMART therapy or with MDI salbutamol plus MDI budesonide (p=0.754).

We also found that SMART therapy were well accepted by most of the patients based on questionnaires answered.

CONCLUSION

From this randomized controlled trial study, it showed that symbicort turbuhaler can be used as an alternative treatment for patients with mild to moderate exacerbation of asthma as there were no significant difference improvements in objective parameters and in subjective parameters compared to nebulized salbutamol.

CHAPTER 1: INTRODUCTION

Asthma is a serious global health problem with an estimated 300 million affected individuals. People of all ages in countries throughout the world are affected by this chronic airway disorder that if uncontrolled, can results in severe daily life limitations and may sometimes be even fatal (GINA, 2008). The prevalence of asthma is increasing in most countries (Weber et al, 2002). In Malaysia, it is estimated about 1.5-1.8 million people are affected by the disease (Malaysian CPG, 2002). Asthma is a significant burden, not only in term of health care cost but also lost of productivity and participation in family life (GINA, 2008). The Second National Health and Morbidity (NHMS II) conducted 1997, shown that asthmatic patients will suffer illness for about 3.7 - 4.6 days of their life for every attack. These indirectly affect their quality of life.

The goal of treatment of acute asthma is to reverse the airflow obstruction, ensure adequate oxygenation and to relieve the inflammation. Administration of short acting β2-agonist like Salbutamol has been commonly used as the conventional reliever in the treatment of patients with acute exacerbations of asthma regardless of whether in outpatient clinic settings or in the emergency departments. Inhaled corticosteroids, on the other hand, are needed for the majority of patients with persistent asthma for their anti-inflammatory effects as asthma is a type I hypersensitivity reaction.

According to the Global Initiative for Asthma Workshop Report (updated 2008), for patients with mild to moderate exacerbations, inhaled Salbutamol, commonly via a metered dose inhaler (and ideally be accompanied with a spacer) may be attempted with 2 – 4 puffs every 20 minutes for the first hour, and subsequently 2 – 4 puffs every three

to four hours for mild exacerbations and up to 6 – 10 puffs every one hour for moderate exacerbations until patient's response is observed. On the other hand, patients with severe to life threatening exacerbations are treated with nebulizer salbutamol (GINA, 2008).

However, recent reviews have shown that, bronchodilator delivered via a metered-dose inhaler, especially when delivered with a spacer (Cates et al, 2006), produces at least an equivalent improvement in lung function as the same dose delivered via nebulizer (Turner et al, 2003).

The recent worldwide severe acute respiratory syndrome (SARS) outbreak and its apparent spread following nebulization has discouraged routine treatment by nebulizer; in some settings, these recent events may facilitate conversion to MDIs with holding chambers (Varia et al, 2003).

In this study, we will attempt to evaluate the use of Symbicort turbuhaler as an alternative reliever medication for mild to moderate acute exacerbation of asthma attack among adult patients that presented to the Emergency Department, Hospital University Sains Malaysia. Subsequently, to evaluate patient's acceptance regarding initiating SMART approach and its effects on asthma control based on asthma control test (ACT) score.

CHAPTER 2: LITERATURE REVIEW

2.1 Definition

Bronchial asthma is defined as a chronic inflammatory airway disorder; this disease is characterized by airway hyperresponsiveness to multiple stimuli and causes recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or early in the morning. These episodes are usually associated with widespread, but variable airflow obstruction within the lung that is often reversible either spontaneously or with treatment (GINA, 2008).

2.2. Pathophysiology

The pathophysiologic hallmark of asthma is an abnormal accumulation of eosinophil, lymphocytes, mast cells, macrophages and myofibroblast that leads to reduction in airway diameter by smooth muscle contraction (bronchoconstriction), vascular congestion, bronchial wall edema and thick secretion, and remodeling of the airway. These changes reflected in pulmonary function changes, increased work of breathing and abnormal pulmonary blood flow (GINA, 2008). Large and small airways often contain plugs composed of mucus, serum proteins, inflammatory cells, and cellular debris. On a microscopic level, airways are infiltrated with eosinophils and mononuclear cells. Evidence of microvascular leakage, epithelial disruption and vasodilation is frequently noted.

For some patients, the development of chronic inflammation may be associated with permanent alterations in the airway structure, referred to as airway remodelling

that are not prevented by or fully responsive to currently available treatments (Holgate and Polosa, 2006).

Inflammation plays a key role in the patophysiology of asthma regardless of disease severity. Inhaled antigen or orther triggers such as allergens, viruses, pollutants (Figure 2.1) will activate immunoglobulin E, mast cell and T-helper cells in the airway and induce the production of the inflammatory mediators and cytokines. In turn, this initiates a cascade of reactions involving lymphocytes, mast cells, eosinophils, dendritic cells, macrophages and epithelial cells that perpetuate the inflammatory response (Figure 2.2). These cells will cause further release of chemokines, cysteinyl leukotrines and nitric oxide. All these mechanisms will cause airway bronchoconsrictions, vasodilatation, and airway edema and mucus hypersecretion. Clearly, the inflammatory process is multicellular, redundant and self-amplifying.

The concepts underlying asthma pathogenesis continue to evolve, especially as various phenotypes of asthma and genetic patterns linked with the disease are identified (Martinez, 2005). Asthma represents a continuum from acute bronchospasm to airway inflammation to permanent airway remodeling. The structural changes associated with airway remodeling, such as subbasement membrane thickening, subepithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, angiogenesis, and mucous gland hyperplasia and hypersecretion, are associated with progressive, nonreversible loss of lung function (Holgate and Polosa, 2006). Therefore, the paradigm of asthma has been expanded over the last 10 years from bronchospasm and airway inflammation to include airway remodeling in some persons (Busse and Lemanske, 2001).

Acute allergic bronchoconstriction results from immunoglobulin E–dependent release of mediators from mast cells. These mediators include histamine, leukotrienes, tryptase, and prostaglandins that directly contract airway smooth muscle (Busse and Lemanske, 2001). Bronchospasm induced by aspirin and other non-steroidal anti inflammatory drugs (NSAIDs) also involves mediator release from airway cells (Stevenson and Szceklik, 2006). Factors regulating airway responses to other stimuli are less well defined but also seem to be related to underlying airway inflammation. Numerous host and environmental factors, such as number and type of infections in childhood, frequent antibiotic use, Western lifestyle, and repeated exposures to allergens, may contribute to the development of allergic asthma.

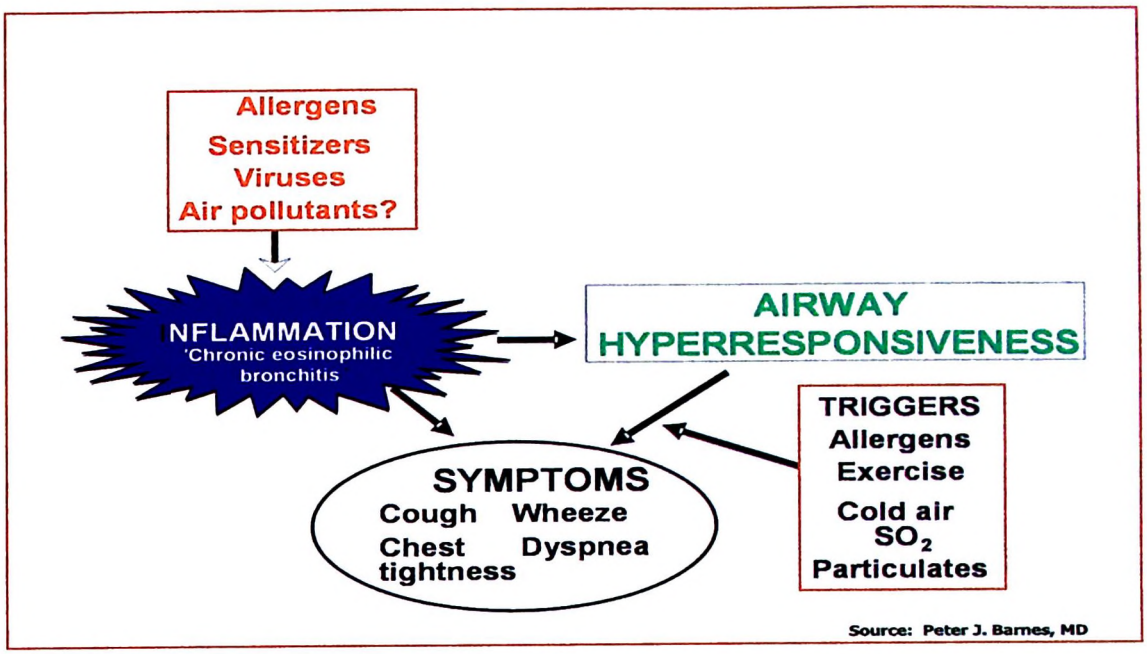

Figure 2.1: Mechanisms leads to asthma inflammation

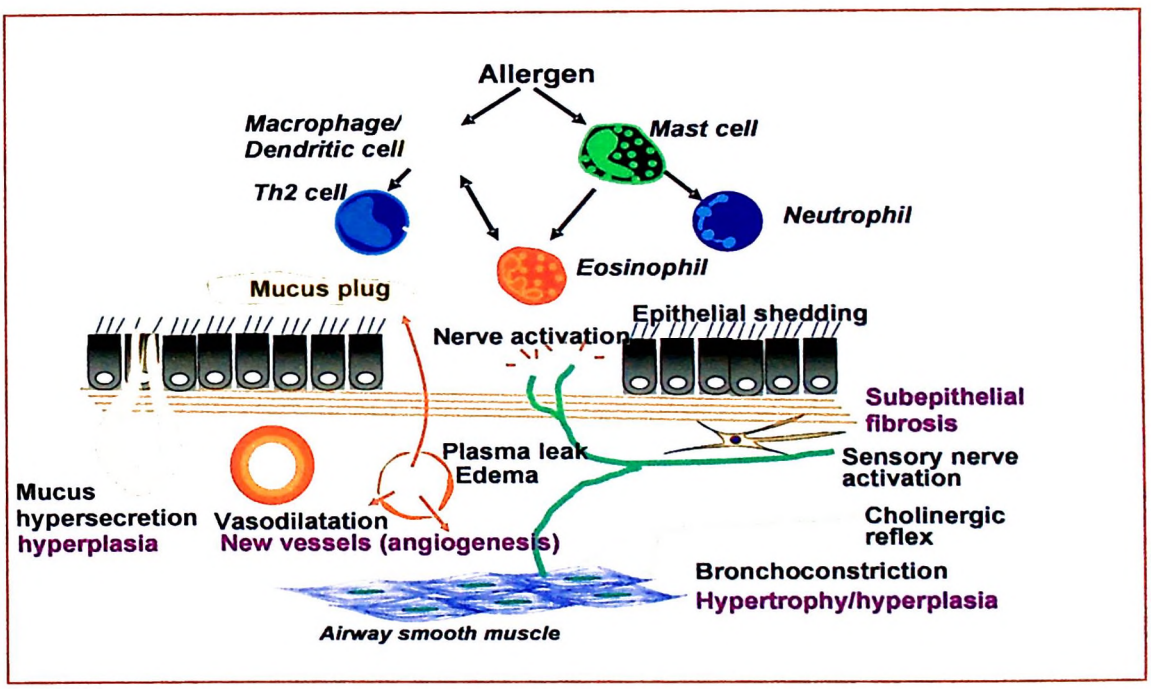

Figure 2.2: Asthma Inflammation: Cells and Mediators involved

Both figures adapted from: Guidelines for the Diagnosis and Management of Asthma, National Heart, Lung, and Blood Institute, 2007.

2.3 Causes of asthma

Viral respiratory infections are among the most common stimuli that invoke acute asthma exacerbation. Increased airway responsiveness secondary to infection may last for two to eight weeks (Busse and Gern, 1997). Exercise is another common precipitant of acute asthma. Unlike other precipitants of acute exacerbation, long-term sequelae are not noted as a result of exercise. Environmental conditions, such as atmospheric pollutants and antigens noted in heavy industrial or densely populated urban areas, are associated with higher incidence and severity of asthma. Indoor antigens, such as mold, house dust mites, cockroaches, and animal dander, are also associated with acute asthma. Occupational exposures, such as metal salt, wood and vegetable dust, pharmaceuticals, industrial chemicals, plastics, biological enzymes, vapors, gases, and aerosols, also may stimulate an asthma attack. As in exercise-induced asthma, exposure to cold air and seasonal changes alone can induce acute bronchospasm.

In Malaysia, there were more cases admitted in month of October, November, January and February than the rest of the months. This data suggest that rainy season caused raised in number of asthma exacerbation as compared with dry season which usually occurred from March to September (Rozlan et al, 1999).

Multiple pharmaceutical agents, such as aspirin, β-blockers (including topical β-blockers), NSAIDs, sulfating agents, tartrazine dyes, and food additives and preservatives, have been implicated in acute asthma. Endocrine factors, such as changing levels of estradiols and progesterone during the normal menstrual cycle and pregnancy, may contribute to the level of airway reactivity (Cydulka, 2006). Emotional stress also can produce an asthma attack.

2.4 Diagnosis

The diagnosis of asthma is usually based on the presence of characteristic symptoms, triad of cough, dyspnoea and wheezing. These symptoms worse particularly at night or early morning and may be associated with chest tightness. It may occur or worsen in the presence of animals, dust, and pollen, changes in temperature and exercise or strong emotional expression. Eczema, hay fever, family history of asthma or atopic diseases is often associated with asthma (Malaysian CPG, 2002).

However, measurements of lung function, and particularly demonstration of reversibility of lung function abnormalities, greatly enhance the diagnostic confidence (GINA, 2008). Measurement of lungs functions provide an assessment of the severity of airflow limitations, its reversibility and variability and provide confirmation of diagnosis of asthma. The term reversibility is generally applied to rapid improvements after treatment and variability refers to improvement or deterioration in symptoms and lung function occurring over time e.g diurnal variability. Obtaining history of variability is an essential component of the diagnosis and assessment of asthma control.

Various methods are available in assessment of airflow limitation, but 2 methods have gained widespread of used in patients above 5 years old. These are spirometry, particularly measurement of force expiratory volume in 1 second (FEV1) and force vital capacity (FVC), and peak flow meter for peak expiratory flow rate (PEFR) measurement (GINA, 2008). Predicted values in FEV1, FVC and PEF based on age, sex and height have been obtained from population studies. The FEV1/FVC less than 0.75 suggest airflow limitation and the degree of reversibility in FEV1 which indicates a diagnosis of asthma is generally accepted as 12% and more or equal 200 ml from the pre-bronchodilator value (Figure 2.3).

A peak flow meter is a small, portable, hand-held device that used to measure airflow in the large airways of the lungs. Specifically, a peak flow meter measures how well air moves out of the lungs. It is an essential for diagnostic and monitoring tool for asthma. The improvement of PEFR of 60 L/min or 20% after bronchodilator or diurnal variation of PEFR more than 20% suggest diagnosis of asthma (GINA, 2008). PEFR usually drops before the asthmatic patients experienced asthma symptoms. Therefore, measuring PEFR regularly will help patients know when the problems are beginning. It also help patients and health care provider to establish a written treatment plan with instruction on how to respond to peak flow readings and guided for dose adjusting. By comparing patient's daily score and personal best score, its can determine the airway condition and help in treatment plan (Marvin D. and Trovato J.). Another benefit of using PEFR monitoring is to determine which factors may worsen asthma. By taking PEFR before and after exposure to allergens or irritants, it can help to identify potential asthma triggers (Marvin D. and Trovato J.).

For patients with symptoms consistent with asthma, but normal lung function, measurements of airway hyperresponsiveness (AHR) to direct airway challenges such as inhaled metacholine and histamine or indirect airway challenges such as inhaled mannitol or exercise challenge may help in establish a diagnosis of asthma (GINA, 2008). Measurements of airway responsiveness reflect the sensitivity of the airways to factors that can cause asthma symptoms, called 'trigger' and the test results are usually expressed as the provocative concentration of the agonist causing a fall of FEV1 20% (PC20). Figure 2.4 showed the graph of airway hyperresponsiveness (AHR) to inhaled methacoline or histamine in a normal subject and in asthmatics with mild, moderate and severe AHR. Asthmatics patients have an increased sensitivity and increased maximal bronchoconstriction response to the agonist. These tests are sensitive for a diagnosis of

asthma but have limited specificity. This means that a negative result can be useful to exclude a diagnosis of asthma but a positive result does not always mean that a patient has asthma. This is because airway hyperresposiveness has been described in patients with allergic rhinitis, bronchiectasis, cystic fibrosis and COPD.

Other methods which will help in diagnosis of asthma are non-invasive markers of airway inflammation and measurement of allergic status. The evaluation of airway inflammation associated with asthma may be undertaken by examining spontaneously produced or hypertonic saline-induced sputum for eosinophilic or neutrophilic inflammation. Level of fraction exhaled nitric oxide (FENO) and fraction exhaled carbon monoxide (FECO) have been suggested as a marker of airway inflammation in asthma. Levels of FENO are elevated in asthmatic patients compared to normal person but these findings are not specific for asthma. Neither sputum nor FENO has been valuated prospectively as an aid in asthma diagnosis but also potential use in determines optimal treatment.

For measurements of allergic status, skin prick tests with allergens represent the primary diagnostic tool. The tests are simple, rapid to perform, low cost and have high sensitivity (GINA, 2008). Specific immunoglobulin E (IG E) measurement also used in assessing allergic status, however it does not surpass the reliability of skin prick test results and cost more expensive. The main limitation of methods to assess allergic status is that a positive test does not necessarily mean that the disease is allergic in nature and causing asthma, as some individuals have specific Ig E antibodies but without any symptoms.

Note: Each FEV_1 curve represents the highest of three repeat measurements

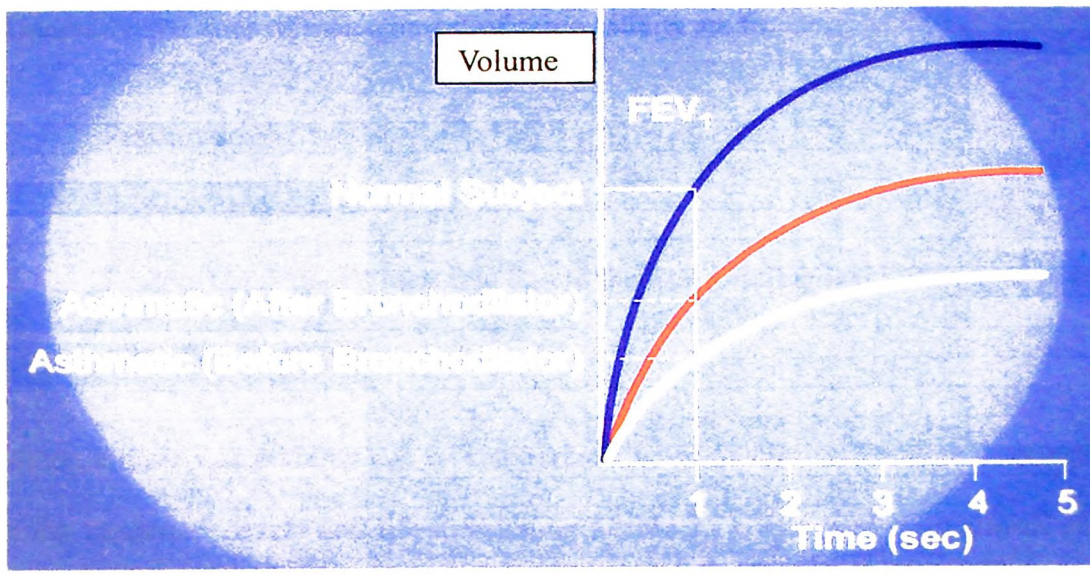

Figure 2.3: Typical Spirometric (FEV_1) Tracings in asthma

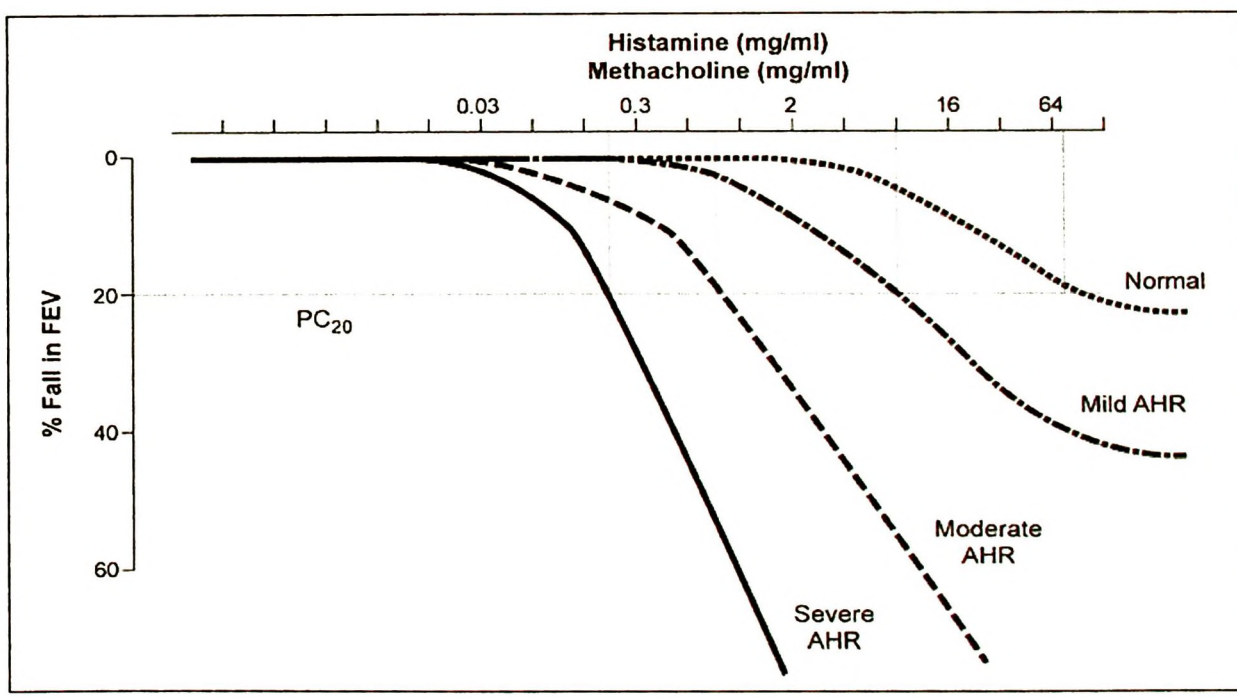

Figure 2.4: Measuring Airway Responsiveness by Methacholine

Both figures are adapted from:

GINA Global Strategy for Asthma Management and Prevention (updated 2008).

2.5 Management of acute asthma

Generally, the aims of management of acute asthma are to:

- Prevent death
- Relieve symptoms
- Restore the patient's lung function to the best possible level as soon as possible
- Prevent early relapse

Acute asthma exacerbation can be categorized based on clinical features. It classified to mild, moderate, severe and life-threatening (Table 2.1). The goal of treatment of acute asthma in the ED is to reverse airflow obstruction (bronchodilator), provide adequate oxygenation, and relieve inflammation.

2.5.1 Bronchodilators

β2-agonists are the mainstay treatment of initial management of acute exacerbation of bronchial asthma. The predominant adrenoceptors in bronchi are β2 type and their stimulation causes bronchial muscle to relax, vasodilatation and skeletal muscles tremor. β2-adrenoceptors activation also stabilises mast cells, thus inhibit mediator release and promote mucociliary clearance. The mechanism of bronchodilator action of β2-adrenergic drugs involves stimulation of the enzyme adenyl cyclase, which, in turn, converts intracellular adenosine triphosphate (ADP) into cyclic adenosine monophosphate (cAMP). This action enhances the binding of intracellular calcium to cell membranes, reducing the myoplasmic calcium concentration, and results in relaxation of bronchial smooth muscle.

The most common side effect of β2-adrenergic drugs is skeletal muscle tremor. Patients also may experience nervousness, anxiety, insomnia, headache, hyperglycemia, palpitations, tachycardia, and hypertension. Commonly use β2-agonists include salbutamol, terbutaline, fenoterol, formoterol and salmeterol. Salmeterol and formoterol is long-acting because its lipophilic side chain anchors the drug in the membrane adjacent to the receptor, slowing tissue washout. According to the Global Initiative for Asthma Workshop Report (GINA, 2008), for patients with mild to moderate exacerbations, inhaled short-acting B2-agonist, commonly via a metered dose inhaler (and ideally be accompanied with a spacer) may be attempted with 2 – 4 puffs every 20 minutes for the first hour. Subsequently, 2 – 4 puffs every three - four hours for mild exacerbations and up to 6 – 10 puffs every one hour for moderate exacerbations until patient's response is observed.

Conventionally, nebulised β2-agonists are used as reliever in the treatment of patients with acute exacerbations of asthma regardless of whether in outpatient clinic settings or in the emergency departments. However, recent reviews have shown that, bronchodilator delivered via a metered-dose inhaler, especially when delivered with a spacer (Cates et al, 2006), produces at least an equivalent improvement in lung function as the same dose delivered via nebulizer (Turner et al, 2003).

Previous studies have reported equipotent dose ratios of beta-agonists delivered by MDI and by nebulizer ranging from 1:1 to 10:1. They found out that with MDI and pear- shaped spacer, the dose that reaches the lungs ranges from 15% to 20% of the total dose (Newman et al, 1984), whereas jet nebulizers deposit only 8% to 10% of the total dose (Newman, 1985). Blake et al in 1992 also compared the effects by the (pre: post) dose ratio of the histamine PC20 (concentration required to decrease FEV1 by 20%)

before and after drug administration. The data suggested that administering 10 puffs from MDI is likely to deliver approximately the same amount of salbutamol as administering 2.5 mg of the nebulizer solution (2: 5 dose ratios).

Furthermore, in the recent worldwide severe acute respiratory syndrome (SARS) outbreak and its apparent spread following nebulization has discouraged routine treatment by nebulizer. In fact, by using human patient simulators (HPS) that can be programmed to different lung conditions, a group of researchers from Hong Kong conducted a study to find out the various dispersion distances of exhaled air and aerosolized droplets during application of a jet nebulizer at different oxygen flow rates (Hui et al, 2009). From that study, it was found that the maximum dispersion distance of smoke particles through the nebulizer side vent was 0.45 m lateral to the HPS at normal lung condition (oxygen consumption at 200 mL/min; lung compliance, 70 mL/cm H2O), but the dispersion distance increases to 0.54 m in mild lung injury (oxygen consumption, 300 mL/min; lung compliance, 35 mL/cm H2O), and beyond 0.8 m in severe lung injury (oxygen consumption, 500 mL/min; lung compliance, 10 mL/cm H2O).

Therefore, healthcare providers have always been advised to take extra protective precaution within at least 0.8 m from patients with febrile respiratory illness of unknown etiology receiving treatment via a jet nebulizer even in an isolation room with negative pressure (Hui et al, 2009). Therefore, whenever nebulization can be avoided, it should be avoided and alternative routes of delivering medications should be sought.

Nonetheless, despite the effectiveness of delivering bronchodilator via the metered dose route (Turner et al, 2003), patient's acceptance of nebulizer Salbutamol is very much entrenched due to its convenience (Varia et al, 2003). In other words, one of the challenges of clinical trials is to translate findings from patient populations studied in the trial into actual day-to-day clinical practice.

Less selective adrenoceptor agonists such as adrenaline (epinephrine), ephedrine, isoetharine, isoprenaline and orciprenaline are less safe, being more likely to cause cardiac arrhythmias. α-adrenoceptor activity contributes to bronchoconstriction but α-adrenoceptor antagonists have not been reported to be effective in practice.

Anticholinergics have been discovered as potent bronchodilators in patients with asthma and other forms of obstructive lung disease, but its action as a reliever medication in acute asthma is less effective than the rapid-acting β2-agonists. Although comparisons of bronchodilator response between anticholinergics and β2-adrenergic agonists have produced conflicting results, the effects of the drugs used in combination are additive (Rodrigo, 2005). This effect is plausible, because anticholinergics affect large, central airways, whereas β2-adrenergic drugs dilate smaller airways.

Anticholinergic drugs competitively antagonize acetylcholine at the postganglionic junction between the parasympathetic nerve terminal and effectors cell. This process blocks the bronchoconstriction induced by vagal cholinergic-mediated innervations to the larger central airways. In addition, concentrations of cyclic guanosine monophosphate (cGMP) in airway smooth muscle are reduced, further promoting bronchodilation. Ipratropium bromide, the synthetic quaternary derivative has replace atropine sulphate because of significant systemic effects. A meta-analysis of

trials showed that combination β_2-agonist and anticholinergic therapy is associated with lower hospitalization rates and greater improvement in PEFR and FEV1 (GINA, 2008).

Theophylline has minimal role in the management of acute asthma. Theophylline, in combination with inhaled β2-adrenergic drugs, appears to increase the toxicity, but not the efficacy of treatment (Parameswaran et al, 2000). Its use is associated with severe and potentially fatal side effects particularly in those on long term therapy with sustained release theophylline and furthermore their bronchodilator effects are less than β2-agonist.

Intravenous magnesium sulphate is indicated in the management of acute, very severe asthma (i.e., FEV_1 <25% predicted), but its usefulness in mild and moderate exacerbation has not been established (Rowe et al, 2000). Although the bronchodilating properties of magnesium sulphate can be helpful, it should not be substituted for standard therapy regimens.

2.5.2 Anti-inflammatory drugs

Corticosteroids are the most effective anti-inflammatory medications for the treatment of persistent asthma. Studies have shown their effectiveness in reducing asthma symptoms, improving quality of life, improving lung function, decreasing airway hyper responsiveness, controlling airway inflammation, reducing frequency and severity of exacerbations (GINA, 2008). The main effects of corticosteroids in acute asthma are only evident after 4-6 hours. Oral therapy is preferred as its effectiveness is equal as intravenous hydrocortisone. A short course of oral corticosteroids for an exacerbation is 40-50 mg daily for 5-10 days depending on the severity of the exacerbation (GINA, 2008). When symptoms have subsided and lung function has

approached the patient's personal best value, the oral corticosteroids can be stopped or tapered down.

The following categories of medications such as leukotriene modifiers e.g montelukast, zafirlukast, 5-lipoxygenase inhibitor (zileuton), mast cell–stabilizing agents (sodium cromoglycate) and anti-Ig E are used as a controller therapy. In terms of the use of any preventative medication (one or more agents from the following groups: inhaled corticosteroids, leukotriene modifiers, or sodium cromoglycate, and edocromil), Asthma Insights and Reality in Asia-Pacific (AIRIAP) study reported only 14.4% of respondents used any preventative medications. Inhaled corticosteroids (ICSs) were the most commonly used preventative medications, in up to 13.6 % of the cases. This is despite the fact that almost half of the sample meeting the criteria for persistent asthma on the basis of self-reported frequency of symptoms. However, fear of side effects was considered to be a major factor in failure to follow the physician's instructions on medication use by over half of the respondents (56.7 %). Other reasons included the concern over long-term use (50.4 % considered it a major factor, and 36.5 % considered it a minor factor), lack of immediate effect (46.8 % and 38.2 %, respectively), loss of effectiveness over time (42.8 % and 41.9 %, respectively), lack of symptoms (37.2 % and 43.2 %, respectively), and cost (30.3 % and 37.0 %, respectively).

Formoterol is a long acting β2-agonist; it has a rapid onset, producing its bronchodilation effect within 1 – 3 minutes of inhalation (Palmqvist et al, 1997) and has duration of action up to 12 hours. Such rapid bronchodilatory effect and long acting effect is comparable with that of Salbutamol, thus making Formoterol suitable for the treatment of acute asthma and to prevent exercise induced bronchospsm (Bateman et al,

2006). In fact, Formoterol has been shown to produce greater lung improvements than Salbutamol over four hours (Bateman et al, 2006). It is because it acts as a full agonist to β2-receptors compared to Salbutamol that acts as partial β2-agonist. The non-bronchodilatory effect of Formoterol are reduced plasma exudation by relaxing the endothelial cells, thus closes the gap. Furthermore, it stabilizes mast cell and reduced neutrophils, thus reduce the releases of reactive oxygen species via the activated neutrophils.

Repeated used of β2-agonists have been shown to downregulate β2-receptors and consequently, it can results in a relative refractoriness to the bronchodilatory effects of this class of drug (Boonsawat et al, 2003; Newnham et al, 1995). On the other hand, high dose of inhaled corticosteroid have been shown to upregulate these receptors and restore the β2-agonist responsiveness (Grove & Lipworth, 1995). The synergistic interactions between the long acting β2-agonists and the inhaled corticosteroids has led to the relatively recent addition of combination therapy of long acting β2-agonist and inhaled corticosteroids in a single inhaler to the armamentarium of asthma therapy. Currently there are two single inhaler combination products available commercially, namely: Budesonide/Formoterol combination (Symbicort tubuhaler) and Salmeterol/Fluticasone combination (Seretide Diskus).

The Budesonide/Formoterol combination in a single inhaler (Symbicort turbuhaler) has recently been shown to be effective as both maintenance and reliever medication (Aziz & Lipworth, 1999). This combination has been used as a novel approach called Symbicort as Maintenance and Reliever Therapy (SMART) approach (O'Byrne et al, 2005). However, although Symbicort has been used in a SMART

approach for both maintenance and reliever in a single inhaler, there is still a paucity of studies done to evaluate its acceptance by the patients in the day-to-day setting. Loh et al in 2008 have done a study to look into the real life effectiveness of SMART approach among Malaysian patients (Loh et al, 2008). In that study, they found that SMART approach is an effective and safe treatment option for patients with inadequately controlled moderate-to-severe asthma in the Malaysian setting.

Since Symbicort has a rapid onset with equal efficacy to Salbutamol; and with the fact that inhaled β2-agonist has been shown to be as effective as its nebulized equivalent, we hypothesize that Symbicort turbuhaler can be used effectively as an alternative reliever therapy to nebulized Salbutamol in emergency department.

The importance of establishing an alternative reliever is further compounded by the need to avoid nebulization and aerosolization in the wake of the surge of respiratory infection epidemics and pandemics such as the Severe Acute Respiratory Syndrome (SARS) and the Influenza A (H1N1) infection. We also attempt to study the subjective part of the treatment, namely the patient's acceptance of this approach in emergency department as many patients who present themselves to the emergency departments, expect to be given some form of therapies that are different from the medications they self-administer at home.

2.6: THE USE OF EXHALED NITRIC OXIDE MEASUREMENTS IN ASTHMA MANAGEMENT

The past few decades have seen a paradigm shift in our understanding of the pathogenesis of bronchial asthma. Rather than seeing bronchial asthma as a bronchohyperreactive airway disease, it is now seen as a T-helper-2 (TH-2) mediated inflammatory disease that involves both the large and small airways (Busse & Lemanske, 2001). In fact, studies performed during these last three decades had shown that distal airways inflammation (airways with less than 2 mm diameter) was a prominent feature in this disease (Martin, 2002).

Conventionally, the diagnosis of asthma is based on history, particularly with the presence of a triad of wheeze, shortness of breath and cough (GINA, 2008). Unfortunately such manifestations are variable. Similarly, the use of serial peak expiratory flow rate or spirometry measurements as well as demonstrating airway reversibility with an increase of FEV1 of at least 12% from baseline 15 minutes post bronchodilator inhalation (GINA, 2008), are based on demonstrating abnormal airway physiology and may often not be present in mild asthma (Smith et al, 2004). Other surrogate or direct markers such as methacholine or adenosine monophosphate challenge tests, as well as fiberoptic bronchoscopy utilizing bronchoalveolar lavage, are time consuming, invasive and uncomfortable for the patients. Two recently proven methods to guide adjustment of asthma management are fraction of exhaled nitric oxide (FENO) and inducing sputum for eosinophilia.

Being a relatively new marker for asthma, nitric oxide (NO) was first described in the 1980s (Zeidler et al, 2004). It was initially known as endothelial derived relaxation factor (EDRF), as it was shown to be responsible for vasodilatation of arterioles (Furchgott & Zawadzki, 1980). Subsequent researches also showed that nitric oxide (NO) played a role in inflammation, immunity and neurotransmission (Zeidler et al, 2004). NO is produced from the conversion of L-arginine to NO and citrulline by nitric oxide synthase (NOS). Constitutive expression of NOS produces low level of NO in healthy lungs. Inducible nitric oxide synthase on the other hand, is responsible for the increased levels of NO produced in inflammatory states in the lung and is markedly upregulated by interferon-γ, tumor-necrosis factor-α, and interleukin-1β and downregulated by corticosteroids (Robbins et al, 2004).

FENO has been shown to be increased in proportion to the severity of bronchial wall inflammation (Payne et al, 2001), severity of airway hyperresponsiveness (Jones et al, 2001; Jatakanon et al, 1998) and its level has been shown to be reduced in a dose dependent manner (Kharitonov et al, 2003; Jones et al, 2002).

Unlike induced-sputum analysis, FENO measurements are easy to perform, reproducible, and were highly accepted by patients (Kharitonov et al, 2003). Conventional tests, as mentioned above, are primarily based on demonstrating abnormal airway physiology, such as bronchial hyperresponsiveness. Therefore, these tests are not sensitive enough particularly in cases of mild asthma. Unfortunately, although conventional tests may show normal results in such cases, it has been shown that, even in asymptomatic asthmatic patients with remission of symptoms of up to one year have been shown to have continued eosinophilic inflammation and bronchial

hyperresponsiveness (Van den Toorn et al, 2000; Van den Toorn et al, 2001; Spallarossa et al, 2003).

In such cases, FENO is particularly helpful, because it has high discriminatory power (Dupont et al, 2003; Malmberg et al, 2003; Deykin et al, 2002). As mentioned, the conventional tests are also time consuming, and may require repeated measurements (for example, in cases of serial peak flow measurements). This may affect patients' compliance (Smith et al, 2008). Dupont et al, 2003 had analyzed the diagnostic value of NO measurements and the ability of the method to differentiate between subjects with airway symptoms and patients with true asthma and it found that a cut-off point for exhaled NO of 16 ppb (parts per billion) gave specificity for the diagnosis of asthma of 90% and a positive predictive value of more than 90%.

In a study by Heffler et al, 2006 involving patients with asthma-like symptoms, which asthma was diagnosed on the basis of 12% improvement in FEV1 after Salbutamol, showed that none of the asthmatic patients had exhaled NO values less than 25 ppb and all the patients with exhaled NO more than 100 ppb were diagnosed with asthma. The sensitivity and specificity of exhaled NO for detecting asthma by using 36 ppb as cut-off point were 78% and 60% and the positive and negative predictive values were 54% and 82%, respectively (Heffler et al, 2006).

Nitric oxide also use as prediction of steroid response (Szefler et al, 2005), steroid dose needed (Kharitonov et al, 2002), monitor response to anti-inflammatory (Silkoff et al, 2001), monitor compliance with anti-inflammatory (Delgado-Corcoran et al, 2004) and monitoring asthma control (Stirling et al, 1998).

In this study, we measure the nitric oxide level by means of the portable, hand-held electrochemical device, [NIOX MINO® Airway Inflammation Monitor; Aerocrine AB, Solna, Sweden] rather than the bulky conventional, stationary chemiluminescence nitric oxide analyzer, [NIOX® Nitric Oxide Monitoring System; Aerocrine AB, Solna, Sweden]. Both NIOX® and NIOX MINO® have been shown to be in clinically acceptable agreement (Alving et al, 2006). NIOX MINO® has also been shown to have good repeatability as well as the obvious added advantage of being a lightweight, portable device (Alving et al, 2006), which makes it the choice for nitric oxide measurement in our study (Figure 4.3).

While the nitric oxide level were measured twice; once, before the patient was enrolled in the study (pre-study monitoring) and another reading at one month after initiation of treatment, during follow-up visit (post-study monitoring). Peak flow meter reading (PEFR), on the other hand, was measured repeatedly as it is simple and inexpensive. It is used to measure dynamic and acute responses after the treatment; it is used to measure both pre- and post-treatments in the emergency department and after each additional dose of treatment as defined in the treatment protocol.

2.7: THE USE OF VISUAL ANALOG SCALE TO MEASURE THE SEVERITY OF DYSPNEA IN ACUTE EXCERBATION OF ASTHMA

Visual Analog Scale (VAS) has been used to grade severity of various symptoms such as abdominal pain, breathlessness in heart failure as well as in asthma. The important concept in determining the significant symptom changes is the concept termed as minimum clinically meaningful change (Anders et al, 2004). The minimum clinically meaningful change in VAS dyspnea score is defined as the mean difference between the first and second VAS scores among patients that report experiencing either "a little less difficulty breathing" or "a little more difficulty breathing (Anders et al, 2004).

In asthma, a study was done by Karras et al, 2000 to determine the minimum clinically meaningful improvements in peak expiratory flow rate (PEFR) and visual analog score (VAS) of dyspnea in patients with acute asthma exacerbation. In that study, VAS of subjects' breathlessness was first assessed at presentation. Asthma treatment was then initiated, and the subjects were re-assessed. During reassessment, subjects were again asked to describe their asthma symptoms as "much better," "a little better," "no change," "a little worse," or "much worse" besides re-evaluating VAS score. Correspondence between self-reported improvement and changes VAS was recorded and analyzed. The mean VAS change among the "a little better" subjects was 2.2 cm (95% CI = 1.1 to 3.4), and this was significantly greater than the -0.4 cm (95% CI = -2.1 to 1.4) change in the "unimproved" subjects (Karras et al, 2000).