THE EFFECTIVENESS OF SALBUTAMOL NEBULIZER ALONE VERSUS SALBUTAMOL NEBULIZER WITH ADDED ATROVENT® IN ASTHMATIC PATIENTS AT EMERGENCY DEPARTMENT HUSM

By

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ABSTRAK

KEBERKESANAN PENGGUNAAN NEBULIZER SALBUTAMOL SAHAJA BERBANDING PENGGUNAAN NEBULIZER SALBUTAMOL YANG DITAMBAH DENGAN ATROVENT® KE ATAS PESAKIT ASMA DI JABATAN KECEMASAN HUSM

OBJEKTIF

Objektif penyelidikan ini adalah untuk membezakan keberkesanan penggunaan nebulizer salbutamol dengan membandingkan penggunaan nebulizer salbutamol yang ditambah dengan Atrovent® ke atas pesakit asma di Jabatan Kecemasan.

KAEDAH

Penyelidikan ini dilakukan secara prospektif dan cubaan klinikal ini adalah secara rambang di Jabatan Kecemasan Hospital Universiti (HUSM) Kubang Kerian, Kelantan. Kesemua pesakit yang terpilih mestilah memenuhi segala syarat yang disediakan dan pesakit mestilah dalam keadaan serangan asthma yang akut. Pesakit yang terpilih akan dibahagikan kepada dua kumpulan, iaitu kumpulan pertama untuk nebulizer salbutamol sahaja manakala kumpulan kedua untuk nebulizer salbutamol yang ditambahkan dengan Atrovent®. Dos salbutamol yang digunakan

adalah 5 miligram manakala Atrovent® ialah 0.5 miligram. Kesemua pesakit yang terpilih sebenarnya adalah pesakit yang datang ke jabatan kecemasan yang mana kemudiannya diberikan nombor. Pesakit yang mendapat nombor ganjil akan ke kumpulan pertama dan yang dapat nombor genap akan ke kumpulan kedua.

Penggunaan nebulizer adalah dengan menggunakan kaedah aliran oksigen diantara 5 – 8 liter seminit. Ukuran pembacaan meter penghembus (PEFR) yang ditentukan akan direkodkan yang mana ianya akan ditentukan pada permulaan (sebelum penggunaan nebulizer) dan juga pada minit ke 30. Parameter klinikal yang lain juga direkodkan seperti kelajuan degupan jantung, tekanan darah dan kiraan pernafasan. Pemerhatian klinikal dilakukan dengan menggunakan mesin pegawasan berjenama Propaq™.

Kesemua data yang diperolehi akan dianalisa dengan menggunakan SPSS® versi 9.0 dan tahap statistik yang 'significant' jika nilai *p* kurang daripada 0.05.

KEPUTUSAN

73 pesakit berumur di antara 13 – 60 tahun diperolehi yang mana min (± SD) 31.19 (14.81) dalam kumpulan pertama dan (± SD) 28.93 (13.85) di kumpulan kedua. Daripada 73 pesakit, 56 pesakit adalah termasuk dalam penyelidikan ini. Daripada jumlah pesakit yang terpilih, 26 pesakit dalam kumpulan pertama dan 30 pesakit dalam kumpulan kedua.

Jumlah rambang ini telah dianalisa secara statistik dan didapati ianya tidak dalam tahap statistik yang 'significant'.

Dari penyelidikan ini didapati:

1. Pembacaan permulaan meter pengukur rintangan hembusan (PEFR) dalam kedua-dua kumpulan tidak menunjukkan tahap statistik yang 'significant' (*p* lebih daripada 0.05).
2. Kedua-dua kumpulan ini menunjukkan peningkatan yang berkesan dalam pembacaan meter pengukur rintangan hembusan dari permulaan pembacaan hingga ke tahap 30 minit dengan tahap *p* kurang daripada 0.05. Bila pembacaan meter pengukur rintangan hembusan yang di perolehi dibandingkan di antara dua kumpulan secara statistik, ianya tidak menunjukkan tahap yang 'significant' (*p* lebih daripada 0.05).
3. Tidak menunjukkan tahap yang bermakna dalam jumlah kemasukan pesakit ke wad.
4. Tidak menunjukkan tahap yang 'significant' dalam pembacaan klinikal seperti kelajuan degupan jantung, tekanan darah, kiraan pernafasan dan saturasi oksigen.

KESIMPULAN

Dalam penyelidikan ini, keputusan yang diperolehi menunjukkan bahawa nebulizer salbutamol sahaja dan nebulizer salbutamol yang ditambah dengan Atrovent® memberikan tindak balas yang memuaskan di mana dilatasi salur pernafasan dan pembacaan meter pengukur rintangan hembusan meningkat (p kurang daripada 0.05). Bila keputusan pembacaan meter pengukur rintangan hembusan di bandingkan dengan kedua-dua kumpulan, di dapati analisa statistik tidak menunjukkan 'significant' (p lebih daripada 0.05). Keputusan penyelidikan akhirnya telah menunjukkan dengan penambahan Atrovent® atau tiada penambahannya ke dalam nebulizer salbutamol tidak akan memberi makna terhadap rawatan serangan asthma yang akut dalam 30 minit yang pertama perawatan.

Didalam penyelidikan ini ianya telah menunjukkan bahawa tiada keberkesanaan klinikal terhadap penambahan Atrovent® bersama salbutamol dengan menggunakan nebulizer terutamanya dalam 30 minit yang pertama di jabatan kecemasan. Walaupun keputusan penyelidikan menunjukkan bahawa penambahan Atrovent® tiada kesan pada 30 minit pertama, seseorang tidak sepatutnya membuat kesimpulan yang mana penambahan Atrovent® dengan salbutamol ini tiada peranan langsung dalam rawatan asthma yang akut.

ABSTRACT

THE EFFECTIVENESS OF SALBUTAMOL NEBULIZER ALONE VERSUS SALBUTAMOL NEBULIZER WITH ADDED ATROVENT® IN ASTHMATIC PATIENTS AT EMERGENCY DEPARTMENT HUSM

OBJECTIVE

The objective of this study is to compare the effectiveness of nebulized salbutamol alone versus nebulized salbutamol combined with ipratropium bromide (Atrovent®) on asthmatic patients presenting to the emergency department.

METHODS

The study is a prospective, single blind, randomized clinical trial conducted at the emergency department, University Hospital (Hospital Universiti Sains Malaysia) Kubang Kerian, Kelantan. Patients were included in the study if they fulfilled the inclusion criteria and presented with acute exacerbation of asthma. The patients were divided into two groups, nebulizer salbutamol alone as group 1 and nebulizer salbutamol with Atrovent® as group 2. The dose used was 5 milligrams for salbutamol and 0.5 milligrams for ipratropium bromide (Atrovent®). Patients were selected in either group by identification on presentation at emergency department

with numbers, patients who received odd numbers belong to group 1 and even numbers belong to group 2.

Nebulization was given by oxygen drive at a flow of 5 – 8 litres per minute and peak expiratory flow rate measurements were recorded at baseline (before nebulizer) and after the first 30 minutes. Other parameters taken for clinical evaluation include heart rate, oxygen saturation, blood pressure and respiratory rate using Propaq™ brand monitor.

The data was analysed using SPSS® version 9.0 with statistical significance taken as *p* value less than 0.05.

RESULTS

A total of 73 patients aged 13 – 60 years old were selected with the mean (± SD) of 31.19 (14.81) in group one and (± SD) of 28.93 (13.85) in group two. Of these, 56 patients were included in the study and the remaining 13 patients were excluded as they did not fulfil the criteria. There were 26 patients in group 1 and 30 patients in group 2 of which 30 were male patients and 26 were female patients. Statistically, the distribution of male and female did not show any significant difference.

From this study it was found that:

1. Peak expiratory flow rate at baseline in both groups was not statistically different (*p* value more than 0.05).
2. Both groups study have shown that it improved significantly in peak expiratory flow rate from baseline to the first 30 minutes of therapy with *p* value less than 0.05, but the peak expiratory flow rate statistically is not significant when the two groups were compared together (*p* value more than 0.05).
3. No significant difference in the number of patients that were admitted to ward.
4. No significant difference in the clinical parameter of heart rate, blood pressure, oxygen saturation and respiratory rate statistically.

CONCLUSION

In this study, the data showed that nebulizer salbutamol alone and nebulizer salbutamol combined with Atrovent® both resulted in bronchodilatation and significant improvements in measured peak expiratory flow rate (*p* value less than 0.05). However, when these results were compared statistically between the two groups, it was not of statistical significance (*p* value more than 0.05). The results showed that adding or not adding Atrovent® had no significance in the treatment of acute exacerbation of bronchial asthma in the first 30 minutes of nebulizer therapy.

This study has shown no benefit to the routine use of a combination solution containing ipratropium bromide and salbutamol when compared with salbutamol alone in the first 30 minutes of therapy. In spite of this, one should not conclude that combination therapy has no role in the treatment of acute asthma.

1 INTRODUCTION

Asthma is a common disease among adults and children. It is well known that asthma is a worldwide disease, with alarmingly high rates of morbidity and mortality. In Malaysia, it is estimated that around two million people have been diagnosed with asthma. Therefore, asthma is a common disease among adults and they can present as a medical emergency, and the number of patients turning up at emergency department will be increased. Malaysian figures have shown an increasing trend of asthma patients attending emergency department that is about 10 percent of the Malaysian population who seek treatment for acute medical illness at emergency department. Medical emergency accounts for about 55 percent of all emergency cases, with acute asthma being the most common medical emergency seen, accounting for about 50 to 60 percent of cases seen per day. Several studies have shown that acute asthma is indeed the commonest medical emergency seen in most of the emergency department all over the nation, representing about 10 to 14 percent of the total number of patients seen daily. This has proven that prompt medical attention is mandatory towards a patient's care especially in handling acute medical illness like asthma in the emergency department.

Management of asthma in emergency department is crucial and need special attention because improper management will lead to over-loading of patients in emergency department and in-patient wards. The main goal of asthma management in emergency department is to relieve the acute exacerbation and prevent further deterioration. The common treatment of acute exacerbation of asthma in emergency department is by inhalation especially by nebulizer with bronchodilator agents. The choice and effectiveness of bronchodilator agents are important in the first step in the acute exacerbation of asthma management. The purpose of this study is to see the effectiveness of the bronchodilator agents used in emergency department to solve the problem of too many patients in a crowded asthma bay and to avoid unnecessary admissions to the ward.

The purpose of the study is to assess the effectiveness of different bronchodilator agents given by nebulizer in the emergency department. In this way, the choice of agents used in nebulizer therapy will help to reduce the length of stay in the emergency department. The question is which bronchodilator agents are ideal to serve this purpose.

The topic of this study was chosen based on other studies done at different centres. The study is specifically designed for the population of Kota Bharu. A number of studies have looked into this issue, with conflicting results. Many practicing doctors believe that the combination of Atrovent® (Ipratropium bromide) with salbutamol is the best therapy in initial asthma

management within the emergency department, even though research evidence is lacking to support one regime over the other.

The topic of this study is to evaluate the effectiveness of the nebulizer salbutamol alone versus nebulizer salbutamol combined with Atrovent® in treating asthmatic patients presenting to the emergency department. We also wanted to see the difference in effectiveness of the nebulizer given in an acute setting in the first 30 minutes of treatment. It is known that salbutamol alone provides good bronchodilatation; however, in combination with Atrovent®, it is not clear if there is any additional bronchodilator effect; and whether this additional effect, if any, is additive or synergistic in nature. In other words, we aim to evaluate the effect of combined Atrovent® with Salbutamol in the early therapy of acute asthma.

This study had its limitations, which had to be overcomed. The study was been done at University Hospital (Hospital Universiti Sains Malaysia) Kubang Kerian. In any emergency department, the first limitation is manpower. It is a well-known fact that within any emergency department, workload does not conform to any fixed rules nor fixed timings. Patient care would always take precedence. Not only was problems encountered regarding manpower in conducting this study, many patients sometimes did not give full cooperation towards the study. Many requested to go back early after feeling better following treatment of nebulizers and thus the duration of the study was affected drastically. The initial aim to monitor the patients half-hourly, for at least 90 minutes of their initial nebulizer therapy

was not possible due to this reason. Due largely to this fact, we were only able to monitor our patients for the initial 30 minutes of therapy. Another limitation was the attitude of patients toward the study. This study gave patients the impression that they were part of an experiment (during the study itself). In the end, many patients refused to participate in the study. The number of the patients involved in the study was also affected. The patients involved were not pre-selected and most of them presented themselves as cases of acute exacerbation to the emergency department.

LITERATURE REVIEW 2

2.1 DEFINITION

Asthma is defined as a condition of airway hypersensitivity and reversible airway obstruction that results in intermittent symptoms of wheezing, dyspnoea, and cough. However, asthma is more than a simple reversible airway obstruction (Busse WW et al, 1993).

Previously, it was believed that asthma referred to almost any sort of difficulty in breathing, especially if it is paroxysmal or episodic. Later in the new recommendations, additions were made related to difficulty in breathing and associations with wheezing. In 1958, a Ciba Foundation Guest Symposium suggested: *Asthma refers to the condition of subjects with widespread narrowing of the bronchial airways, which change in severity over the short periods of time either spontaneously or under treatment, and it is not due to cardiovascular disease. The clinical characteristics are abnormal breathlessness, which may be paroxysmal or persistent, wheezing, and in most cases is relieved by bronchodilator drugs* (Ciba Foundation, 1959).

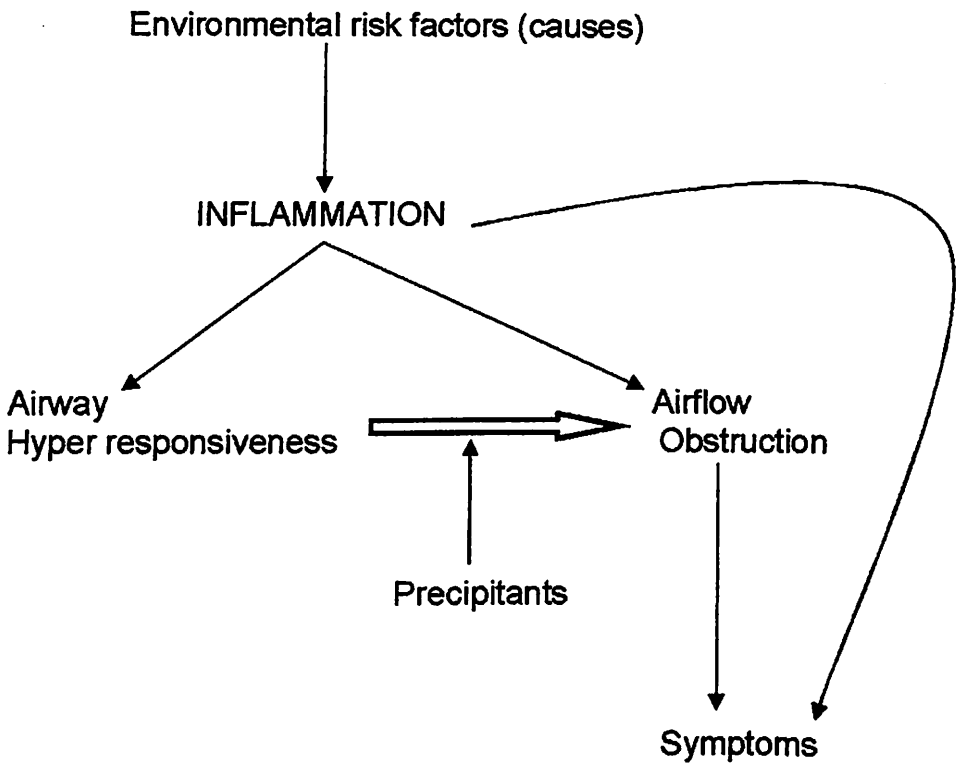
In 1962, The Committee on Diagnostic Standard of the America Thoracic Society suggested: *Asthma is a disease characterized by an increased responsiveness of the trachea and bronchi to a variety of stimuli and manifested by widespread narrowing of the airways that changes in severity either spontaneously or as a result of therapy. Asthma, as defined may occur in subjects with other bronchopulmonary or cardiovascular diseases, but in these instances the airway obstruction is not causally related to these diseases* (American Thoracic Society Committee on Diagnostic Standards, 1962).

Current thinking and new research developments have changed the definition of asthma. Asthma is characterized also by paroxysmal spasmodic narrowing of the bronchial airways due to inflammation of the bronchi and bronchial smooth muscle contractions. The inflammation component is central to the pathogenesis of symptoms, bronchoconstriction and airway hyper-responsiveness leading to dyspnoea and wheezing. Also inflammation can be characterized by oedema, infiltration with inflammatory cells especially eosinophils, hypertrophy of glands, smooth muscle and damaged epithelium. These will result in the state of hyper-responsiveness where airways narrow easily in respond to wide range of stimuli (Holgate ST and Finnerty JP, 1988), which is presented clinically as sign, and symptom of coughing, wheezing, chest tightness and shortness of breath. They are often worst at night and the symptoms are called 'attack '. The airway narrowing is usually reversible but in some patients with chronic

asthma the inflammation may lead to irreversible airway obstruction (Roche WR et al, 1989).

A working definition of asthma should include underlying airway inflammation with its physiological correlation and bronchial hyper-responsiveness [**figure 2.1**]. The clinician, physiologist, immunologist, and pathologist all may have different perspectives on asthma definition. The merging of this different perspective into an acceptable definition of asthma has begun to occur and is important for more specific and effective treatment of this disease.

Based on current knowledge, a working definition of asthma is: *Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a vital role particularly, mast cells, eosinophils, T-lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyper-responsiveness to a variety of stimuli* (National Heart, Lung and Blood Institute, 1995).



Adapted from Stephen T. Holgate, M.D., D.Sc.

Figure 2.1: Mechanisms Underlying the Definition of Asthma

2.2 PATHOPHYSIOLOGY OF ASTHMA

Asthma, whatever the severity, is a chronic inflammatory disorder of the airways. This has implications for the diagnosis, management, and potential prevention of the disease. Pathogenesis of asthma is related to each other, which are divided into three components, that is:

1. Airway inflammation
2. Airway obstruction
3. Airway hyper-responsiveness

2.2.1 Airway inflammation

The airways of asthma patient are infiltrated by a number of different inflammatory cells, which then cause complex interactions resulting in epithelial disruption and mucosal oedema. An initial trigger in asthma may cause the release of inflammatory mediators from the bronchial mast cells, macrophages, and epithelial cells. These substances cause the directed migration and activation of an inflammatory infiltrate composed predominantly of eosinophils and neutrophils. Chemical substances like leukotrienes are then released and they will further attract cellular infiltrates. This event will produce epithelial injury, abnormalities in neural mechanism, and increase in airway smooth muscle responsiveness and airflow obstruction.

Epithelial injury can lead to increased permeability and sensitivity to inhaled allergens, irritants, and inflammatory mediators. Furthermore, transudation of fluid and reduced clearance of inflammatory substances and respiratory secretions occur with disruptions of epithelium mucocilliary mechanism. This process may lead to chronic irritation of the airways. The illustrated diagram (**figure 2.2**) will show the event of the inflammation that occurs in asthma patient, which contributes to airway inflammation (Busse et al, 1993).

2.2.3 Airway obstruction

Airflow limitation in asthma is recurrent and caused by a variety of changes in the airway. These include:

1. Acute bronchoconstriction.

   Allergen-induced acute bronchoconstriction results from an immunoglobulin-E dependent release of mediators from the mast cells that includes histamine, tryptase, leukotrienes, and prostaglandin (Marshall and Bienenstock, 1994), which directly contract the airway smooth muscles. Aspirin and other non-steroidal anti-inflammatory drug can also cause acute airflow obstruction in some patients and evidence indicates that non-Immunoglobulin-E dependent response also involves mediator release from airway cells (Fisher et al, 1994).

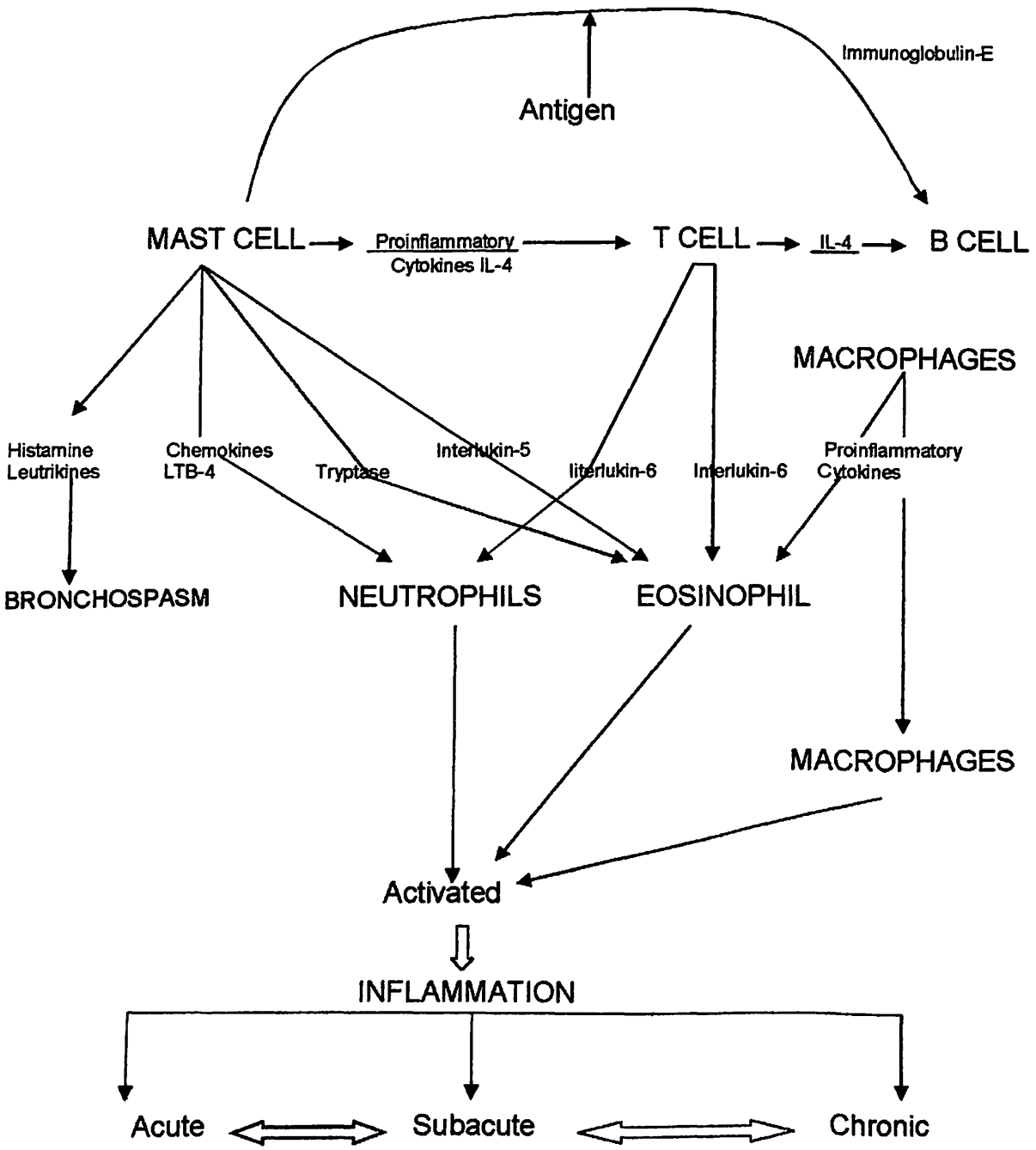


Figure 2.2: CELLULAR MECHANISMS INVOLVED IN AIRWAY INFLAMMATION

(James and Kay, 1995)

Other stimuli including exercise, cold air and irritants can cause acute airflow obstructions. This mechanism is unknown but the intensity of the response appears related to underlying airway inflammation (Busse et al, 1993). Stress to can play a role in precipitating exacerbation of asthma although the exact mechanism is still unclear. It is postulated that this involves enhanced generation of proinflammatory cytokines (Friedman et al, 1994).

2. Airway oedema

Airway wall oedema, even without smooth muscle contraction or bronchoconstriction, limits airflow in asthma. Increased micro-vascular permeability and leakage caused by the released mediators also contribute to mucosal thickening and swelling of the airway wall. As a consequence, swelling of the airway wall causes the airway to become more rigid and interferes with airflow.

3. Chronic mucus plugs formation.

In severe intractable asthma, airflow limitation is often present. In part, this change may arise as a consequence of mucus secretion and the formation of inspissated mucus plug.

4. Airway remodelling.

In some patients with asthma, airflow limitation may be only partially reversible. The aetiology of this component is not as well studied as other features of asthma but may relate to structural changes in the airway matrix that may accompany longstanding and severe airway inflammation. There is evidence that a main histological feature of asthma in some patient is an alteration in the amount and composition of the extra cellular matrix in the airway wall (Djukanovic et al, 1990; Laitinen and Laitinen, 1994). As a consequence of these changes, airway obstruction may be persistent and not responsive to treatment. Regulation of this repair and remodelling process is not well established, but the process of repair and its regulation are likely to be key events in explaining the persistent nature of the disease and limitation of response to therapy. The above postulation suggests a rationale for early intervention with anti-inflammatory therapy.

2.2.4 Airway hyper-responsiveness

An important feature of asthma is an exaggerated bronchoconstriction in response to wide variety of stimuli. Airway hyper-responsiveness leads to clinical symptoms of wheezing and dyspnoea after exposure to allergens, environmental irritants, viral infections, cold air, or exercise. Research indicates that airway hyper-responsiveness is important

in the pathogenesis of asthma and that the level of airway responsiveness usually correlates with the clinical severity of asthma.

The importance of the airway inflammatory response to airway hyper-responsiveness is substantiated by several observations. First, airway markers of inflammation correlate with bronchial hyper-responsiveness. Second, treatment of asthma and modification of airway inflammatory markers not only reduce symptoms but also diminish airway responsiveness. Some investigators have shown that although anti-inflammation therapy reduced airway hyper-responsiveness, it did not eradicate it. A small study found that control of airway inflammation did not control bronchial hyper-responsiveness (Lundgren et al, 1988). From this, it may be concluded that some other factor, in addition to inflammation, contributes to airway hyper-responsiveness.

2.3 DIAGNOSIS

Diagnosing asthma is the first step towards effective treatment. Studies show that up to half of all asthmatics do not receive proper treatment because they do not recognise the signs, and so they suffer needlessly. However, there are also cases where people have been misdiagnosed with asthma and received unnecessary treatment. This is particularly common in children who have a greater tendency to wheeze because their airways are small and their immune response involves mucus as a major factor. Two-thirds of infants under one year old who wheeze with respiratory infections ultimately do not develop asthma.

Making a correct diagnosis is extremely important, so as correct treatment can then be followed. Diagnosis guideline is necessary and the key indicators are listed below.

2.3.1 Key Indicators for Diagnosing Asthma

1. Wheezing is a high-pitched whistling sound that occurs when breathing out especially in children (A normal chest examination does not exclude asthma) and history of any of the following:

(i) Cough, worse particularly at night

(ii) Recurrent wheeze

(iii)Recurrent difficulty in breathing

(iv)Recurrent chest tightness

Note: Eczema, hay fever, or family histories of asthma or atopic diseases are often associated with asthma, but they are not key indicators.

2. Symptoms may occur or worsen at night, awakening the patient. Symptoms that occur or worsen in the presence of:

(i) Exercise

(ii) Viral infection

(iii) Exposure to animals (especially with fur)

(iv) Exposure to domestic dust mites (in mattresses, pillow, upholstered furniture, carpets)

(v) Smoke (tobacco, wood)

(vi) Pollen

(vi) Changes in temperature

(vii) Strong emotional expression (laughing or crying hard)

(viii) Aerosol chemical

3. Revisable and variable airflow limitation as measured by using a peak expiratory flow meter in any of the following way:

(i) Peak expiratory flow rate increased more than 15 percent at least 15 to 20 minutes after inhalation of a short acting beta-2 agonist, or

(ii) Peak expiratory flow rate varies more than 20 percent from the morning measurement upon arising, to another measurement 12

hours later in patients on bronchodilator therapy (more than 10 percent in patients who are not on bronchodilator therapy), or

(iii)Peak expiratory flow rate decreases more than 15 percent after 6 minutes of running or exercise.

4. Diagnostic challenges include the following:

(i) Young children whose primary symptom is cough or who wheeze with respiratory infections are often misdiagnosed as having bronchitis or pneumonia (including acute respiratory disease – ARI) and those ineffectively treated with antibiotics or cough suppressants. Treatment with asthma medication can be beneficial and diagnostic.

(ii) Asthma should be considered if the patient's colds repeatedly "go to the chest" or take more than 10 days to clear up, or if the patient improves when asthma medication is given.

(iii)Tobacco smokers and elderly patients frequently suffer from chronic obstructive pulmonary disease with symptoms similar to asthma. Yet they may have asthma and may benefit from treatment. Improvement in peak expiratory flow rate after asthma treatment is diagnostic.

(iv)Workers who are exposed to inhalant chemicals or allergens in the workplace can develop asthma and may be misdiagnosed as having chronic bronchitis or chronic obstructive pulmonary disease. Early recognition (Peak expiratory flow rate measurements at work

and home), strict avoidance of further exposure, and early treatment are essential.

These indicators are useful in diagnosing asthma and if any of the indicators are present, the patients can be considered asthmatic.

2.4 MANAGEMENT OF ASTHMA

The aims of management in asthma can be divided into:

i. to recognize asthma

ii. to abolish symptoms (relieve respiratory distress)

iii. to restore normal or best lung function as soon as possible

iv. to reduce morbidity and prevent mortality

The management of asthma depends on how we approach and educate asthmatic patients. Other important steps that are required in managing asthma are avoidance of precipitating factors and finally, drug therapy. These drugs are bronchodilators and anti-inflammatory drugs, commonly used in the emergency department especially for the relief of symptoms in the acute attack. Much research has been done regarding the efficacy of bronchodilators used in an acute attack and many researchers have analysed and compared the effectiveness of different bronchodilators either used alone or in combination.

2.5 Bronchodilators of beta adrenergic

The initial management of acute asthma exacerbation in children and adult in the setting of an emergency department focuses on the rapid relief of bronchospasm with inhaled or nebulized bronchodilators. Beta-2 agonists are the most effective of the bronchodilators owing to their rapid onset of

action and the extent of achieved bronchodilatation (Sears MR, 1992). Anticholinergic agents, such as ipratropium bromide (Atrovent®) and atropine sulphate, have a slower onset of action and weaker bronchodilating effect than beta-2 agonists but may relieve cholinergic bronchomotor tone and decrease mucosal oedema and secretions (Gross NJ, 1988).

Beta-2 agonists

These drugs are the most effective bronchodilators available. The beta-2 agonists are the fastest and most efficacious medication to help alleviate bronchospasm in the acute asthmatic and are clearly the treatment of choice. Beta-2 agonists are catecholamine derivatives that act via an accumulation of cyclic AMP in the cells thus causing relaxation. They should be considered the main therapeutic intervention for the asthmatic patient. While the beta-2 agonists relax bronchial smooth muscle, they also help decrease bronchospasm and constriction, and help inhibit the release of inflammatory mediators. Additionally, they appear to increase ciliary's movement. They are several ways that these agents can be administered including oral, subcutaneous, via metered-dose inhalers, and via nebulizer.

The oral route is less useful in acute situations and the most common route in the emergency department is via inhalation. They are safe drugs with few side-effects when taken by inhalation or nebulizer. The

therapeutic effect is felt within minutes of inhalation. The main side-effects are tremor and tachycardia. Examples of inhaled or nebulized beta-2 agonist are salbutamol, terbutaline, fenoterol, salmeterol.

The effect of this drug on the bronchodilatation is dose-dependent, which larger doses result in a more sustained effect (Barnes PJ and Pride NB, 1983). Asthmatic patients usually show the largest response to beta-2 agonist but the magnitude of effect depends on pre-treatment airway calibre, dose, route, and method of administration.

Selective beta-2 agonists given by metered-dose-inhalers or in the nebulized form are the bronchodilators of choice in patients with asthma and other forms of reversible airway obstruction in maintenance therapy or in acute attack. The need for treatment and its effects should be monitored by measurements of peak expiratory flow rate or force expiratory volume in one second (Spirometry). The monitoring of asthma patients after treatment by using peak expiratory flow rate is the best way to see the improvement and the assess the need for further intervention and proper follow-up as out-patients or in-ward patients.

In severe cases of asthma, a subcutaneous form of beta-adrenergic therapy may be appropriate. Generally, the subcutaneous route do not offer any advantage over the inhaled route unless the patient is unable to take a nebulizer or has not responded to inhaled medication. Thus, patients with

altered mental status, or those in extremis, may be given subcutaneous doses of adrenaline, Ventolin®, or Terbutaline®. Obviously, in older patients the risks of giving these medications must be weighed against the possibility of inducing dysrhythmias or myocardial ischaemia. If a pregnant patient is being treated, terbutaline is a better choice, as adrenaline has been associated with birth defects. The dose of terbutaline is 0.25 milligrams (up to 0.5 milligrams) in adults. In critically-ill patients, intravenous beta-agonists can be considered if all other measures have failed.

The beta-2 adrenergic receptors

Adrenergic receptors are classified into beta-1, beta-2, and beta-3 receptors. In the lung, there are beta-1 and beta-2 receptors present and the bronchodilator action is mainly mediated via the beta-2 receptor. These beta-2 agonists in the lung produce their effect by interaction with specific beta-2 adrenergic receptors located in the plasma membrane of virtually all types of cell. The receptor consists of the protein that traverses the cell membrane seven times, forming three extra cellular, and three intracellular loops. Binding of the beta-2 agonists will activate cyclic-AMP, the intracellular second messanger, ultimately producing the physiological response that leads to bronchodilatation. A characteristic of many membrane-associated receptors, including beta-2 adrenergic receptors, is desensitisation after high dose or repeated exposure to the agonists. After

prolonged exposure, the number of receptors in the plasma membrane is reduced, due to decreased production of the messenger RNA for the receptors (down regulation) (Hadcock JR and Malborn NB, 1988). Up regulation of the receptor occurs as a result of increased production of messenger RNA. This is due to an increase in the transcription of the gene for the receptor, which is stimulated by glucocorticoids and thyroid hormones. Other non-bronchodilators functions of the beta-2 adrenergic agonist include: enhanced mucocilliary clearance, inhibition of cholinergic neurotransmission, suppression of micro-vascular leakage, inhibition of mediator release from mast cells and basophils, and inhibition of release of mediators from other inflammatory cells.

Routes of administration

Beta-2 adrenergic bronchodilators can be administered orally, by inhalation, subcutaneous or intravenous injection. The inhalation route is preferred almost without exception because the side-effects are fewer for any given degree of bronchodilatation. Inhalation is as effective as parenteral administration for treating acute, severe attacks of asthma in most patients, although some who have severe bronchial obstruction may benefit initially from parenteral therapy.

Oral preparation still has some role in the treatment of children too young to use a metered-dose inhaler conveniently. Sustained-release oral

preparations reduce nocturnal asthma, but they are not as effective for this purpose as the long acting inhaled beta-2 adrenergic agonists.

The use of nebulizer to deliver bronchodilators was formerly the standard practice for young children, in the emergency department treatment of patients with acute, severe asthma and for the treatment of hospitalised patient. All these indications have been challenged, where the beta-2 adrenergic agonist therapy delivered under supervision via a metered-dose inhaler with a spacer device is as effective in the emergency department setting as therapy with the nebulizer for both adults and children. In hospitalised patients, therapy with metered-dose inhalers is as effective as nebulizer treatments and results in considerable financial savings. Even in small children, the nebulizer may be replaced by metered-dose-inhalers with a spacer device and an attached mask.

Potential adverse reaction to beta-2 adrenergic agonist

Adverse reactions of the beta-2 adrenergic can be divided into those that result from the expected pharmacological actions of the drugs and those that could not be predicted from these properties.