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Review Article

Asthma & COPD

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Abstract

Asthma & COPD are the 2 major respiratory diseases that are widespread globally, though big differences between them exist in regard to their pathophysiology and treatment. The main treatment modalities for the two diseases are the inhalation routes of administration. The use of the inhalational routes of administration for the drugs used for the management of asthma and COPD is justified by many advantages such as the low effective dose, faster onset of action and lower systemic side effects. However, some advantages for these routes also exist. The major disadvantage is the technique of use, which many patients do not master even with repeated sessions of teaching by the healthcare providers. Difficulty in applying and following the correct inhalers use was found to be a major reason for patients' non-adherence and consequently failure of the treatment plan.

Keywords: asthma; copd; low effective dose

1. Introduction

1.1 Asthma and COPD definition

Respiratory diseases are widespread among the population due to many factors including lifestyle and heredity. Asthma and chronic obstructive pulmonary disease (COPD) are among the most common respiratory diseases that afflict millions of people worldwide and cause significant morbidity and mortality

The World Health Organization (WHO) has predicted that 235 million people suffer from asthma and more than 3 million people die from COPD each year [43]. Both diseases are characterized by obstructive airway limitation and inflammation, but they differ in the inflammatory cells, pathophysiology, and signs & symptoms [45].

Asthma is a chronic heterogeneous disease that attacks the lungs causing inflammation that result in exaggerated airway narrowing which is fully reversible. Asthma affects all ages, but often occurs during childhood [29]. The most common symptoms of asthma are chest tightness, shortness of breath, coughing and wheezing sound during breathing. However, these symptoms occur in different degrees according to the severity of the disease [31]. These symptoms are not very specific for the disease, so their availability does not confirm the disease. Hence, diagnosis of asthma should be done thorough medical history, physical examination and evaluation of lung function. There is no obvious cause of asthma, but there are some environmental and genetic factors that increases the risk of developing asthma and precipitating its attacks. The most common triggering agents that could cause allergy and precipitate asthmatic attacks are house dust mites, cockroaches, animal fur, mold and pollens and non-allergic causes include cigarette smoke, exercise and cold air [29]. Additionally, genetic factors are a major risk to developing asthma in children if one or both parents have a history of atopic disease [7].

Chronic obstructive pulmonary disease (COPD) is a progressive airway limitation that is irreversibly characterized by an abnormal inflammation response caused by significant exposure to noxious particles or gases leading to narrowing in small airways that result in hyperinflation of the lungs. COPD could present in two major types, which are chronic bronchitis and emphysema[45]. It affects adults and the elderly, but it is more prevalent in the elderly according to national data that shows the prevalence in the adult-only 1% while it is much more in people aged ≥40[10]. Smoking is the major risk factor for the development and progression of COPD and up to 90% of all death from COPD are because of cigarette smoking. However, environmental exposure, genetic predisposition and history of asthma also increase the risk of developing COPD. The major symptoms of COPD is chronic cough that could be accompanied with sputum, dyspnea and exercise intolerance. These symptoms are worsened by exacerbation and lead to wheezing, chest tightness, tachycardia and fever. As COPD progresses it is associated with different comorbidities such as cardiovascular disease, osteoporosis, lung cancer and sleep disorders [45].

Although asthma and COPD have similar clinical manifestations, they differ in their characteristics. Example of this is the cough that is usually dry and mostly worse at night in asthma, this could occur in COPD only after many years of smoking. On the other hand, in asthma paroxysmal dyspnea is characterized by shortness of breath, while in COPD this occurs early in this disease with physical exercise, but at rest later. In addition, the release of inflammatory mediators is broader in asthma than COPD. In asthma the elevated level of T-helper cell type-2 in the airways releases certain cytokines, including interleukin (IL-4, IL-5, IL-9 and IL-

13) that result in eosinophilic inflammation and immunoglobulin E (IgE) production. While inflammasome, T1 and T17 are activated by neutrophils in COPD [29][5].

However, there is no cure for both diseases other than avoiding triggering agents, but the pharmacological treatment can ameliorate the quality of life, reduce the number and severity of exacerbations and manage the symptoms [44] [45].

1.2 Inhalational therapy advantages and challenges

Administration of drugs into the body can be via various routes like oral, intravenous, inhalational, transdermal. Each route of these has its special features, advantages and disadvantages [38]. The selection of the route of administration is taking into account the characteristics of the health problems treated and the properties of the drug [38].

In relation to the chronic respiratory diseases such as asthma and COPD, the ideal route of drug administration is the inhalational route or sometimes called the aerosol route. The preference of the inhalational route here is due to the plentiful advantages which are gained in the inhalational treatment compared to the other routes of administration [3][4][30].

The goal of inhalational therapy in respiratory diseases is to provide a localized treatment that potentially achieves several benefits and overcomes some disadvantages [3]. By delivering the drug directly to the lung, which is the target organ, this affords a higher drug concentration at the target organ compared with that reaching the circulatory system. This is in contrast to the drug administered orally or parenterally, and hence lower drug doses is required in inhalation dosage forms to produce the same therapeutic effect or even better compared with the systemic routes of administration. Additionally, administering the dose directly results in less systemic absorption thus reducing the risk of adverse side effects [9][30]. In summary, inhaled drugs produces the high pulmonary efficacy with lower doses and fewer systemic side effects [4][9]. In addition, inhaled drugs are rapidly absorbed due to the lung's large surface area (about 80- 140 m2) and the alveolar epithelium's low thickness (about 0.1 and 0.5 mm). Hence, inhalation of the drugs provides a rapid onset of action, like what is seen in inhaled salbutamol which takes a few minutes to give its relief effect [4].In contrast to the oral administration, inhalational rout of administration provides the opportunity for the drug to bypass the first-pass hepatic metabolism and to be exposed less to the degradation enzymes[38]. By excluding the IV administration and for the drugs with small molecules, inhalation is the quickest route of administration[3].

However, there are hurdles to inhalational therapy to give its best. One of the challenges in the delivery of drugs by inhalational route is the defense approaches of the respiratory system, which are represented in mechanical, chemical, and immunological barriers. These barriers prevent the drug particles from reaching the target, which is mainly the pulmonary epithelium, by either expelling them out of the respiratory system or inactivating them [21]. Another important challenge which is related to the patient's behavior is the proper use of the inhalation device, where improper inhaler technique can prevent the successful delivery of the drug to the lung and prevent getting the full benefit from the inhalation route [21]. In addition, the good adherence to inhaled therapies by patients is another challenging [21]. Regarding financial issues, experts found that the expense of inhalation therapies also poses a challenge [30].

1.3 Pharmacological management of respiratory diseases

There are numerous drugs available for the management of asthma, COPD, and other respiratory diseases like pulmonary fibrosis, acute pneumonia, seasonal allergy, cystic fibrosis, and Bronchiectasis. These drugs are classified into several pharmacological classes depending on their mechanism of action such as bronchodilators, anti-leukotriens, muscarinic antagonist, corticosteroid and anti-IgE antibodies.

The bronchodilators are the most commonly used drugs for the management of asthma and COPD. They work by dilating the bronchial airways and relaxing the liner muscles. They are divided into four categories looking at their onset of action and duration: short-acting B2 adrenergic agonists (SABAs), long-acting B2 adrenergic agonists (LABAs), anticholinergics, and xanthine derivatives. SABAs have rapid onset of action which takes seconds to minutes, reaching the maximum action within approximately 30 minutes and lasts for 4 to 6 hours. This sort of medications are used on as-needed basis for the relief of acute asthma. The foremost common and useful drug of this category is Salbutamol (Albuterol). Conversely, Salmeterol and formoterol are examples of LABA medications that afford an extended duration of action of approximately 12 hours and need to be used regularly. It may be accustomed to treating chronic asthma, COPD patient and reducing moderate and severe COPD relapses. additionally, inhaled ipratropium is that the most popular example of the anticholinergics, which works by blocking the muscarinic acetylcholine receptors. It has around 45 minutes onset of action, with a maximum impact within 60 to 90 minutes and a half-life of 6 to 8 hours[35]. Furthermore, ipratropium is used as an alternate therapy for patients who are intolerant or can't use SABA.

Inhaled corticosteroids (ICS) are the most widely used drugs for the management of asthma and COPD. They may be used alone or in combination with other pharmacological classes. It acts by reducing the potent inflammatory mediator and diminishing airway inflammation[25]. As the disease progresses, the utilization of two or more drugs may be more effective in the management of the disease. Nowadays, there are combination inhaler devices that contain two or more drugs from different pharmacological classes and thus improve the patient's medication adherence. Inhaled corticosteroid and long-acting beta- 2 adrenergic agonist or short-acting beta -2 adrenergic agonist (ICS / LABA or ICS / SABA) combinations are often used. Moreover, the short-acting beta-2 adrenergic agonists (SABA) and short-acting anti-muscarinic antagonists (SAMA) combination can be used. Additionally, long-acting beta-2 adrenergic agonists (LABA) with Long-acting anti-muscarinic antagonist (LAMA) can also be used to treat COPD and severe asthma patients[24].

Drugs used for the management of respiratory disorders can be administered via many types of inhalational devices. So, respiratory physicians must be careful in choosing the correct inhaler for the patient taking into consideration the patient ability to use the device correctly and also the device efficacy for every patient condition as there's no specific inhaler device that suits all patients[32]. Studies have shown that the most commonly used inhalational devices are pressurized metered-dose inhalers (pMDI) and dry powder inhalers[40]. By applying pressure, a pressurized metered-dose inhaler converts the drug from a solution or suspension formulation into liquid[19]. pMDIs exist in two categories: extra-fine aerosols and also general pMDI. General pMDI consists of a container, actuator, and a metering valve. These are usually multi-dose, portable, and compact devices and available for treatment of many respiratory illness because of their advantages that include straightforward use, high accuracy and affordable cost[23][40]. Extra-fine aerosol devices are often used for low-dose drugs which have a smaller particle size because side effects increase as the particle size increases[40].

Dry powder inhaler devices contain drugs in powder form[19]. They are available in four main types; First, the single-dose devices that have the drug within a hard gelatine capsule form that should be inserted in the device before each dose. Second type are the DPI disposable devices that contain pre-metered doses that are discarded after use. Third are the multiunit devices that have individual doses pre-metered in the replaceable blisters, disks, dimples, or tubes. Fourth DPI inhalers are

those with multiple-dose reservoirs that contain a bulk amount of medication powder with a built-in mechanism that measures a single dose when actuated, and individual doses are delivered when the device is actuated. A multi-unit inhaler should ensure more precision dosage control as well as chemical stability of the formulation than a multiple-dose type, but it is more expensive [16]. The use of the DPIs is quite common among respiratory diseases patients because it has minimal drug sedimentation and requires less coordination compared to pMDI, so it's the foremost preferred device for elderly, children, and patients with poor inhalation techniques[11]. However, a dry powder inhaler requires extra care regarding storage because it encompasses a high sensitivity to humidity.

Soft mist inhalers (SMIs) are the new form of inhalers that include the drug in the form of propellant-free liquid that's moved slowly through a nozzle system [13]. They are compact, multi-dose devices that have high fine particle fraction and lung deposition, but they may not be preferred to use by patients since it is hard to prepare the first doe, has fewer drug doses compared to other inhaler devices, and require significant breathing coordination[12][6].

1.4 Correct inhaler technique and errors

In order to maintain the disease control, achieve maximal clinical benefit, enhance disease outcome and improve quality of life, it is necessary to use the inhaler correctly. Mastering the inhaler technique would reduce the drug's adverse effects, disease exacerbations, treatment costs, morbidity, and mortality rates[18][25][33][37][39]. Pressurized metered dose inhaler (MDI), dry powder inhaler (DPI) and soft mist inhaler (SMI), which are the three main inhaler types, have similar administration techniques despite the differences in design and shape. The standard technique for use starts from device preparation to inhalation until completion. For MDI, it is recommended that the patient stand or sit up straight with head titled back little initially, remove the inhaler cap and shake it subsequently. Then, the patient should exhale comfortably and completely. After that, he/she should put the inhaler's mouthpiece in the mouth, between teeth and lips closed around, ensuring that the inhaler is upright or at a correct position. Thereafter, he/she should inhale deeply and slowly while pressing down the inhaler canister. Afterward, he/she should hold the breath as much as possible or for 5-10 seconds and next, exhale slowly. Finally, the mouthpiece should be replaced straight away. The patient should note to keep a gap between repeated doses with shaking the inhaler repetitively. These steps are also utilized for MDI if used via a spacer, and also for the DPIs, and SMIs; however, slight differences exist. As per MDI with a spacer no need for coordination between pressing the inhaler and inhaling, there can be 1-2 seconds apart between the actuation and the inspiration. For SMI, an additional step is needed before starting the treatment to prepare the inhaler for use, which is holding the inhaler upright and turn the base in the orientation of the arrows until it clicks. In contrast, DPIs are available in different models which differs in the preparation process and drug administration. However, the administration technique is standard for all DPI designs. Both MDI and SMI require loading before their first use and if they are not used for a long period, one puff need to be sprayed in the air to prepare the inhaler for use. However, DPI and SMI don't require shaking or waiting between repeated doses and they are not used with a spacer [25].

A high portion of inhalers users are making errors regardless of the device type. These were found to be approximately 90 % of patients[39]. Studies have shown some discrepancies in the classification of errors. Some categorize the errors into critical and non-critical errors, while others classify them according to the inhalation technique and device-related errors. Critical errors are the errors that impede drug deposition in the lungs, resulting in little or no medication delivery, thus reducing the effectiveness in the disease management[18][33][39]. Whereas non-critical errors are the errors that might lead to inadequate drug delivery to the lungs[39]. On the other hand, inhalation technique errors are the patient's wrong action to transfer the drug from the device to the target organ beginning with complete exhalation before inhalation until breath holds on. Whereas device-related errors encompass handling the device wrongly before and after inhalation as preparing the device, dose, or handling completion[18]. In COPD patients, studies found that 45% made at least one error when using their inhaler, 50% were related to the device, 31% were related to the inhalation technique, and 19% were related to both [18]. In asthma patients, the most common errors in MDI users are device-related, particularly coordination; meanwhile, in DPI users, inhalation-related errors are the most common errors, particularly insufficient inspiration[33][37].

1.5 Factors affecting the inhaler technique

For effective management of asthma and COPD three vital components must be considered. These are patient, drug, and device, as there is a relationship between each component, the suitability of the drug to the patient, the patient and technique of using the device, the device and drug delivery. These components complement each other to achieve maximum efficacy and stability to the patient [34]. There are many factors that can influence the technique and its validity among inhaler users, such as patient's age (as seen in elderly and children), gender, number of inhalers used, adequate information and education received about the inhalers , patient self-inhalational technique, and bronchodilator response rate [41]. Of these, patient's age, gender, educational level, number of devices prescribed, and instructions given about inhalers are the most common factors contributing to 36% of inhaler error frequency [27].

Dust, chemical agents, air pollution, biomass fuel, and wood burning are among the factors that influence the development of COPD, but smoking is the most common factor affecting the stability of COPD patients [8]. Smoking has a negative impact on the stability of the patients with asthma and other respiratory diseases. Approximately 36% of emergency department patients with asthma exacerbations are current smokers. There is also a possibility of negative effects of smoking on asthmatic patients even after smoking cessation [15]. Additionally, body mass index (BMI) is one of the factors that might affect the patient condition and proper inhalation technique, as patients with a BMI of 35 who are considered obese are more likely to make one or more inhalation errors than patients with a normal BMI of less than 30 [2]. The type of inhaler plays a role in the inhalation process, and errors have been observed in patients who use metered dose inhalers (MDI) more frequently than in dry powder inhalers (DPI)[26]. To prove this, a study was conducted to evaluate the handling of COPD patients with 6 common inhalers to know the percentage of errors in inhalation technique for each inhaler. This study showed that MDI has the highest error rate while DPI has the lowest error rate [27].

Frequent educational sessions help to develop skills in the technique of inhalers use, with approximately 90% of patients gaining good skills after two educational sessions, regardless of the type of inhaler. In addition, elderly patients require more educational sessions than other patients to ensure that the inhaler is used correctly[14]. Nurses as well as all health care providers have a significant and visible impact on disease stabilization and control by providing adequate patient education, counseling, and awareness [34]. In addition, proper education, and training on how to use the inhaler is an important factor in increasing patient awareness and decreasing errors, as the error rate at the first patient assessment visit in a study was high, but after the second and third visits the error rate decreased very clearly, and this indicates the importance and role of education in improving inhaler use, reducing errors, and providing more effective medications[1].

1.6 Adherence to inhalers use

Adherence refers to patient's willingness to follow a treatment plan. Adherence to an inhaler prescription necessitates obtaining the

prescription swiftly and using the inhalers exactly as prescribed, including dose, dosing interval, treatment duration, and any additional instructions given by the physician and pharmacist. Patients should be instructed to inform their physician if they stop using their inhaler or modified their usage, but this is rarely done by patients which could lead to losing control of the condition. According to several studies, COPD therapy regimens have failed to deliver optimal results, with drug non-adherence and poor inhaler technique cited as the major reasons[20][28]. According to World Health Organization (WHO) non-adherence to asthma medications is caused by a variety of reasons. These reasons may be classified into five main categories: socioeconomic, condition-related, treatment-related, healthcare system-related, and patient-related factors [42].

Adherence to the treatment plan could fail at any time. The three distinct temporal phases of non-adherence include failure to begin treatment, failure to administer therapy appropriately, and non-persistence with treatment. In most circumstances, initiating dose is a binary occurrence, with patients either starting or not starting to take their medication. The degree to which a patient's follows their prescribed dosing plan over time, from start to finish, is the second step and called implementation. This means adhering to the medication's instructions, which in the case of asthma includes using an inhaler. Persistence - the last stage - is defined as the continuation in using the drug from the time between the start of therapy and the end of treatment. Following this, there may be a period of non-persistence until the targeted prescription duration is completed[17]. As a solution for the inadequate control of respiratory disorders, a number of novel treatments are now accessible for patients suffering from severe uncontrolled conditions. According to practice recommendations, clinicians should address medication adherence and inhaler technique before initiating one of these treatments, in addition to profiling the asthma condition. As a result, before prescribing any additional drugs for the patient, physician need a clear means to identify those with poor asthma control related to trouble with adherence or inhaler technique[36].

In contrast to asthma, COPD patients were reported to have a very high rate of non-adherence. A study done at the Respiratory Center of Bach Mai hospital, a major hospital in Northern Vietnam Showed that large computerized axial tomography (CAT) scores, short COPD durations, low modified medical research council (mMRC) grades, extended hospital admissions, and a high number of exacerbations have all been connected to incorrect inhaler usage and poor drug-adherence [22]. Non-adherence to COPD medications has been shown in other studies to impair clinical and financial results, making non-adherent patients a focus for cost-effective treatment. To improve adherence, physicians should discuss therapeutic decisions with patients and consider lifestyle factors, demographic characteristics, co-morbidities, physical limitations, psychological and cognitive status, and pharmacological factors (polypharmacy issues) when choosing the best inhaler device. As a result, the therapy and equipment may be adjusted to the specific needs and preferences of each patient [11].

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