WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 6.647
Volume 7, Issue 2, 783-789 Research Article ISSN 2278 – 4357

REVIEW OF DETERMINANCE AND OVERVIEW TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE(COPD)

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Article Received on
06 Dec 2017,

Revised on 28 Dec. 2017,
Accepted on 18 Jan. 2018,

DOI: 10.20959/wjpps20182-10817

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a respiratory disease characterized by chronic airway inflammation, a decline in lung function over time, and progressive impairment in quality of life.[1] In chronic obstructive pulmonary disease (COPD), airflow is obstructed during expiration. This increases the work of breathing and causes dyspnea. In contrast to asthma, the airflow obstruction is not reversible and usually progresses over time. There are several mechanisms of airflow obstruction in COPD. Chronic bronchitis results in hypersecretion of mucus which fills and obstructs the airway lumen. Inflammation and fibrosis of the airway mucosa and surrounding tissue (obliterate bronchiolitis) cause airway wall thickening. Emphysema causes loss of the alveolar attachments which normally hold the airway open.[2]

RISK FACTORS

Risk factors for COPD

- **Genes**

COPD is a polygenic disease and a classic example of gene-environment interaction. The genetic risk factor that is best documented is a severe hereditary deficiency of alpha-1 antitrypsin,[4] a major circulating inhibitor of serine proteases. This rare recessive trait is most commonly seen in individuals of Northern European origin.[5] Premature and accelerated development of panlobular emphysema and decline in lung function occur in both smokers and nonsmokers with the severe deficiency, although smoking increases the risk appreciably. There is considerable variation between individuals in the extent and severity of the emphysema and the rate of lung function decline. Although alpha-1 antitrypsin deficiency is

relevant to only a small part of the world's population, it illustrates the interaction between genes and environmental exposures leading to COPD. In this way, it provides a model for how other genetic risk factors are thought to contribute to COPD.[6]

- **Exposure to particles**

1. Tobacco smoke (10 pack Years; 50% smokers develop COPD):

Tobacco Smoke: Cigarette smoking is by far the most commonly encountered risk factor for COPD. Cigarette smokers have a higher prevalence of respiratory symptoms and lung function abnormalities, a greater annual rate of decline in FEV1, and a greater COPD mortality rate than nonsmokers. Pipe and cigar smokers have greater COPD morbidity and mortality rates than nonsmokers, although their rates are lower than those for cigarette smokers.[7] Other types of tobacco smoking popular in various countries are also risk factors for COPD[8,9] although their risk relative to cigarette smoking has not been reported. The risk for COPD in smokers is dose-related.[10] Age at starting to smoke, total pack-years smoked, and current smoking status is predictive of COPD mortality. Not all smokers develop clinically significant COPD, which suggests that genetic factors must modify each individual's risk.

Passive exposure to cigarette smoke (also known as environmental tobacco smoke or ETS) may also contribute to respiratory symptoms 11 and COPD20 by increasing the lungs' total burden of inhaled particles and gases.[12,13] Smoking during pregnancy may also pose a risk for the fetus, by affecting lung growth and development in utero and possibly the priming of the immune system.[6]

2. Indoor air pollution from heating and cooking with Biomass fuel in poorly ventilated homes (at least 25 years of exposures).

3. Occupational dusts, organic and inorganic: (attributable Risk 15% in American population)

a. Automobile-drivers, vehicular mechanics, fertilizer manufacturing, chlorinated organic compounds dyes, explosives, rubber products, metal etching, plastics, ammonia exposure in refrigeration and petroleum refining, grain dust and funguses in farmers, textile mill manufacturing, leather manufacturing, food products manufacturing and sales, beauty care workers and welders in automotive industries.

b. Exposures to crystalline silica: cement industry, brick manufacturing, pottery and ceramic work, silica sand, granite and diatomaceous earth industries, gold mining, and iron and steel founding

4. Outdoor air pollution

• Reduced Lung volumes:

1. Lung growth and development

2. Previous Tuberculosis (28-68% cases of post-treated TB; 2.9-6.6 folds' increase risk)

3. Early childhood Recurrent Lower Respiratory infections (2-3-fold risk). 4. Poor Nutrition

- Female Gender (reason not known)
- Old Age (physiological obstruction)
- Low-Socioeconomic status (Multi component).[3]

MECHANISM OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE:

Chronic obstructive pulmonary disease involves inflammation of the respiratory tract. In COPD, there is a predominance of neutrophils, macrophages, and cytotoxic T-lymphocytes (Tc1 cells). The inflammation predominantly affects small airways, resulting in progressive small airway narrowing and fibrosis (chronic obstructive bronchiolitis) and destruction of the lung parenchyma with destruction of the alveolar walls (emphysema). These pathological changes result in airway closure on expiration, leading to air trapping and hyperinflation, particularly on exercise (dynamic hyperinflation). This accounts for shortness of breath on exertion and exercise limitation that are characteristic symptoms of COPD.[14]

ROUTES OF DRUG DELIVERY TO THE LUNGS

Drugs may be delivered to the lungs by oral or parenteral routes and also by inhalation. The choice depends on the drug and on the respiratory disease.

Inhaled Route

Inhalation is the preferred mode of delivery of many drugs with a direct effect on airways, particularly for asthma and COPD. It is the only way to deliver some drugs such as cromolyn sodium and anticholinergic drugs and is the preferred route of delivery for β_2 agonists and corticosteroids to reduce systemic side effects. Antibiotics may be delivered by inhalation in patients with chronic respiratory sepsis (e.g., in cystic fibrosis). Inhalation is also used to facilitate systemic drug delivery in other diseases (e.g., to avoid daily injections with insulin.) The major advantage of inhalation is the delivery of drug to the airways in doses that are

effective with a much lower risk of systemic side effects. This is particularly important with the use of inhaled corticosteroids (ICS), which largely avoids systemic side effects. In addition, drugs such as inhaled bronchodilators have a more rapid onset of action than when taken orally so that more rapid control of symptoms is possible.[14]

Delivery Devices

Several ways of delivering inhaled drugs are possible[15] taken orally so that more rapid control of symptoms is possible.

A. Pressurized Metered-Dose Inhalers.

B. Spacer Chambers.

C. Dry Powder Inhalers.

D. Nebulizers.

Oral Route

Drugs for treatment of pulmonary diseases may also be given orally. The oral dose is much higher than the inhaled dose required to achieve the same effect (typically by a ratio of ~20:1), so that systemic side effects are more common. When there is a choice of inhaled or oral route for a drug (e.g., β_2 agonist or corticosteroid), the inhaled route is always preferable, and the oral route should be reserved for the few patients unable to use inhalers (e.g., small children, patients with physical problems such as severe arthritis of the hands). Theophylline is ineffective by the inhaled route and therefore must be given systemically. Corticosteroids may have to be given orally for parenchymal lung diseases (e.g., in interstitial lung diseases), although it may be possible in the future to deliver such drugs into alveoli using specially designed inhalation devices with a small particle size.

Parenteral Route

The intravenous route should be reserved for delivery of drugs in the severely ill patient who is unable to absorb drugs from the GI tract. Side effects are generally frequent due to the high plasma concentrations.

Overview of Pharmacological Treatment in COPD

Apart from oxygen, no drug has been shown to reduce the increased risk of death in patients with COPD. For this reason, drugs are prescribed predominantly to reduce symptoms, improve functional capacity, and prevent and treat exacerbations. Drugs are prescribed in a stepwise fashion. Mild symptoms can be managed with an inhaled short-acting beta agonist

(SABA), taken when needed either before exercise or for the relief of exertional breathlessness. Patients who need inhalations several times a week are likely to benefit from adding a long-acting muscarinic antagonist (LAMA) or a long-acting beta agonist (LABA). The choice of second-line drug depends on the patient's response and preference. While there are few clinically important differences between the LAMAs, there are differences between LABAs which may be more obvious to patients, and are important in affecting their choice. Most importantly, formoterol, indacaterol and vilanterol have a relatively fast onset of action, of 5–10 minutes, while salmeterol has a 30-minute onset. These differences may not be important once patients are taking long acting bronchodilators regularly. Like salmeterol, formoterol and indacaterol, the newly available LABAs vilanterol and olodaterol have statistically and clinically significant effects on lung function, exercise tolerance, SABA use, dyspnoea, quality of life and exacerbations. LABAs are well tolerated and there are negligible differences between them in relation to adverse effects. Tremor and tachycardia appear to occur less commonly with LABAs than SABAs. LAMAs include tiotropium, umeclidium, glycopyrronium and aclidinium. There are only small differences between them in efficacy. The duration of action of aclidinium is shorter and therefore it is the only LAMA prescribed in a twicedaily regimen. These drugs have adverse effects which include urinary retention in patients with prostatic enlargement, worsening of glaucoma and atrial arrhythmias. While these effects had a very low prevalence in clinical trials, most studies have excluded patients at risk, so it is difficult to know the true prevalence of these adverse effects in the general population of patients with COPD. In a large safety study of tiotropium with cardiac end points, there was no increased mortality or major adverse cardiac effects with tiotropium 5 microgram or 2.5 microgram inhaled daily for a median of one year.[14]

Combination bronchodilator therapy

Combining broncho- dilators with different mechanisms and durations of action may increase the degree of bronchodilation for equivalent or lesser side effects. For example, a combination of a short-acting 2-agonist and an anticholinergic produces greater and more sustained improvements in FEV1 than either drug alone and does not produce evidence of tachyphylaxis over 90 days of treatment.[6]

The combination of a 2-agonist, an anticholinergic, and/ or theophylline may produce additional improvements in lung function and health status. Increasing the number of drugs usually increases costs, and an equivalent benefit may occur by increasing the dose of one

bronchodilator when side effects are not a limiting factor. Detailed assessments of this approach have not been carried out.[6]

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