Pharmacology and therapeutics of adult asthma: role of the pharmacist in the follow-up of adult asthma patient

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ABSTRACT: This review aims to describe the pathophysiology, pharmacology and therapeutics of asthma and to explore pharmacist role in the follow-up of adult asthma patient. Asthma is one of the most prevalent chronic diseases worldwide, thus constituting a major public health problem. The high prevalence of this disease is a challenge for the health professionals, especially for the pharmacist. Given the complexity of this disease, it is important to understand the immunological and neurological mechanisms underlying its pathophysiology. Immunologically, asthma is a type I hypersensitivity mediated by immunoglobulin E (IgE), being developed in two phases: the first consisting of the contact with the allergen or sensitization phase, and the second occurring after the second contact with the allergen. The mechanisms of neurogenic inflammation are not yet fully understood, being the most accepted hypothesis that bronchial hyperresponsiveness results from a series of changes in the autonomic nervous system. Asthma therapy has the goal to promote long-term control and the relief of acute asthma attacks. The pharmacist has an important role involving the patient in disease self-management and also promoting a proper adherence to therapy.

KEYWORDS: Asthma, Pharmacology, Pharmacy

INTRODUCTION
Asthma is a chronic inflammatory disease of the airways characterized by a general bronchial obstruction. In the presence of certain stimuli, airways present a hyperactivity resulting from the inflammation, broncospasm, altered contractility of smooth muscle and remodelling, this is, the thickening and dislocation of the bronchial epithelium [1-6].

Asthma is associated with great morbidity, affecting about 300 million people around the world, with a higher prevalence and incidence in developed countries [1, 7-11]. Epidemiologic studies refer a growing tendency of allergic diseases in its different clinical manifestations in the last decades, including asthma, rhinitis, hives and atopic eczema, with a prevalence between 15% and 30% of the population [12, 13]. In December 2010, the Coordinating Commission of the Asthma Control National Program revealed the results from the first National Survey of Asthma Control, which consisted in the study of the prevalence of asthma in Portugal and of the proportion of asthmatic patients with controlled disease. The results showed that asthma affects about 10% of the Portuguese population and about 57% of the asthmatic patients have the disease controlled, demonstrating a significant reduction in mortality rate [14].

According to the etiology, asthma is ranked in extrinsic and intrinsic. Extrinsic asthma is considered a multifactor disease that results from an interaction of the individual, particularly its genetic profile, with the environment. Therefore, the contact between individuals genetically predisposed and certain etiological agents can trigger the development of asthma. These agents are known as allergic, like mites, animals and pollens, and non-allergic, such as physical exercise, smoke, pollution and climate changes. This type of asthma occurs generally in children and young adults, being triggered by an antigen-antibody reaction in mast cells. These individuals are generally associated with family history of allergic disease, such as rhinitis and eczema, and manifest the disease seasonally, according to the exposure to etiological agents [1, 8]. Intrinsic asthma usually manifests in adults being triggered by an imbalance in the autonomic nervous system [1]. Considering the frequency and the gravity of asthma attacks, this disease is ranked in intermittent, mild persistent, moderate persistent and severe persistent and it is determined by the degree of inflammation, broncospasm and remodelling, represented by the symptoms, nocturnal symptoms and by the peak expiratory flow [15]. However these are the main classifications for asthma, there are several other types that don’t fit in these classifications, such as occupational asthma, asthma related to exercise and several others.

PATHOPHYSIOLOGY OF ASTHMA
Asthma as a multifactor chronic disease requires management. Therefore it is essential to understand the pathophysiology of this disease [5].

As previously mentioned, asthma is essentially classified in extrinsic and intrinsic. Given the higher prevalence of extrinsic asthma and the complexity of the underlying mechanisms, the immunological mechanisms will be first described and then the neurological mechanisms of asthma [1, 4].

Immunological mechanisms
Immunologically, asthma is a type I hypersensitivity, mediated by IgE [16, 17]. Generally, it develops in two phases: the first one consists of the contact with an allergen, also called sensitization phase, and a second one that occurs
after the second contact with the allergen, which can be divided into early and quick response or delayed response [17, 18]. When the individual contacts with a certain allergen for the first time, phase called sensitization, it is recognized by antigen presenting cells, such as macrophages and dendritic cells. This type of cells presents the allergen, in the context of the major histocompatibility complex, to T lymphocytes which release inflammatory mediators, like interleukins (IL) 2 and 4. This release will stimulate T-helper cells 1 and 2, respectively. T-helper cell 2 cells secrete IL-5, IL-4, and IL-13, that will stimulate, on one hand, eosinophils and basophils, the release of chemokines and metalloproteases, and, on the other hand, B cells, producers of immunoglobulins, especially IgE, which will attach to FcεRI receptors, present in the surface of mast cells and basophils. These receptors are high affinity receptors for the region Fc or crystallized fragment of IgE and consist of a complex tetramer that includes four chains: one α chain, one β chain and two γ chains [2, 16, 17, 19-26].

Figure 1 - Interaction between FcεRI and an antigen (Available from Wikipedia, http://en.wikipedia.org/wiki/Fc_receptor, accessed January 2012).

After the second contact with the allergen, this stimulates IgE molecules on mast cells and basophils surface to produce a quick response exacerbated with the release of intracellular mediators of inflammation such as histamine, proteases, leukotrienes, prostaglandins, chemotactic factors, among others [17, 19, 20, 24, 28].

Because IgE molecules are present in great number at the mast cell surface, adjacent IgE molecules recognize antigen determinants of the same allergen, which triggers a complex mechanism of massive degranulation of mast cells [21]. The connection of the allergen to IgE molecules promotes stimulation of FcεRI receptors (Figure 1), activating tyrosine protein kinase, which converts phosphatidylserine decapeptide to phosphatidylserine and metalloproteases, such as major basic protein and eosinophils cationic protein. These metalloproteases exert a toxic effect on epithelial cells, promoting cell death [2, 17, 18, 20, 33-36].

Then, it is triggered the remodeling process of the airways, characteristic of persistent asthma. The synthesis of growth factors promotes an increase in the smooth muscle mass, the number of mucus producer goblet cells, the number of glandular cells and promotes vascular proliferation, which leads to airway obstruction. Simultaneously there is an increase in fibroblasts capable of synthesizing collagen, fibronectin and tenascine that will lead, in turn, to airway fibrosis. This process becomes a cycle that leads to a continued deterioration of the airway [2, 17, 37-47]. New findings on pathophysiology of asthma have described the importance of an interaction of bronchial epithelium cells with mesenchymal elements, such as fibroblasts. Thus, the bronchial epithelium has been recognized as a potential target for the development of new therapeutics [26, 48-52].

Neurogenic mechanisms

The nervous system divides into central nervous system and peripheral nervous system. The peripheral nervous system subdivides into sensory division or afferent and motor division or efferent. In asthma pathophysiology it is involved the autonomic part of the motor division of peripheral nervous system, also called autonomic nervous system. This is subdivided into parasympathetic and sympathetic systems. Although parasympathetic nervous innervation largely excels sympathetic innervation, the respiratory tract has a great sympathetic activity, namely through β2 subtype adrenergic receptors [53, 54].

At a respiratory level, peripheral nervous system intervenes in the regulation of the caliber of the vessels, bronchi and larynx, in mucus secretion and many others. This regulation is possible due to the existence of sensory receptors, which detect for example stretching in the smooth muscle, and nerve endings called C fibers in the lower respiratory tract. The detection stimuli are integrated by peripheral nervous system and it is produced a response on smooth muscle and blood vessels, present in bronchi walls [20, 53, 55].

Parasympathetic system is subdivided in cholinergic system and non-adrenergic and non-cholinergic system (NANC). Generally, cholinergic system, whose main neurotransmitter is acetylcholine (ACh), mediates bronchoconstriction by stimulating muscarinic receptors M2.
Asthma is a disease characterized by periods of exacerbation alternating with asymptomatic periods, which distinguishes asthma from other obstructive pulmonary diseases. Thus it can be difficult to diagnose asthma. In a first approach, there are several data important to take into account such as medical history, family history, signs and symptoms and even the environment that surrounds the patient. Once this data is collected it is important to perform diagnostic exams as routine laboratory exams, sputum study, respiratory function tests, chest radiographs, electrocardiogram to screen for complications of asthma in the heart, allergy tests to identify possible etiological agents particularly in extrinsic asthma, in which must be performed the study of markers of inflammation such as eosinophils, triptase among others [1, 8, 20, 80]. Leukotrienes antagonists are frequently used drugs in asthma related to exercise and in mild to moderate asthma in patients that do not respond to inhaled corticosteroids. Generally, these drugs promote a reduction of the symptoms and a slight improvement in respiratory function. The more common side effects are headaches, upper respiratory tract infections such as pharyngitis, fever, arthralgias, myalgias, dizziness and dry mouth, among others [20, 81]. Cromones are drugs that prevent the mast cell degranulation and therefore have a weak anti-inflammatory effect, being used in the prophylaxis of exercise induced asthma. Because they are inhaled drugs, the main side effects include broncospasm and irritant cough [6, 20, 80, 81]. Ketoilfen is another drug whose mechanism of action involves the mast cell and is similar to the one of the cromones, preventing mast cell degranulation. This is an oral drug so the main systemic side effects are drowsiness, dry mouth and increased appetite [20, 81].

### Table 1. Drugs used as control therapy (Adapted from Fredvás et al. [1]).

<table>
<thead>
<tr>
<th>Therapeutic group</th>
<th>Examples of drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled corticosteroids</td>
<td>Beclometasone, Budesonide, Fluticasone</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Methylprednisolone, Prednisone, Dexametazone</td>
</tr>
<tr>
<td>Leukotrienes antagonists</td>
<td>Zafirlukast</td>
</tr>
<tr>
<td>Cromones</td>
<td>Sesamum terebinthaceum, Nohemoni saxa</td>
</tr>
<tr>
<td>Long acting β-adrenergic agonists</td>
<td>Salbutamol, Formoterol, Proterol</td>
</tr>
<tr>
<td>Methylxanthines</td>
<td>Aminophylline, Diprophyline, Thespyline</td>
</tr>
<tr>
<td>Muscarinic antibody</td>
<td>Omalizumab</td>
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### ASTHMA THERAPY

Asthma is a disease that results from a combination of chronic inflammation of the airways and bronchoconstriction. Thus treatment should cover several areas as anti-inflammatory therapy and bronchodilator therapy, respectively, and also the prevention of the exposure to etiological agents. Because asthma is characterized by intermittent manifestations of the disease, therapy has the goal to promote long-term control and the control of acute attacks [1, 8, 79].

Control therapy

Control therapy operates differently from the relief therapy and the goal is the treatment of the inflammation of the airways. Thus, this therapy promotes a long-term control of the symptoms helping to prevent asthma attacks [8, 79]. In Table 1 is presented a list of the more common drugs used in the control therapy of asthma.

The most commonly used drugs as control therapy are the inhaled and oral corticosteroids. This group of drugs inhibits intracellular cascades that lead to the production of cytokines and other inflammatory mediators, promoting the reduction of the edema and mucus secretion, indirectly leading to bronchodilation. Because these drugs act in the cell nucleus, corticosteroids therapy take some time to have effect therefore being used only for control therapy. Inhaled corticosteroids are used mainly in persistent asthma presenting some side effects such as dysphonia, irritating cough and oral candidiasis. Oral corticosteroids are more used in cases of severe persistent asthma, with side effects like osteoporosis, neurological disorders, obesity and hypertension, among others [1, 8, 20, 80].

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Relief therapy

Relief therapy has as main goal the bronchodilation during an asthma attack. Therefore, the sooner these drugs are administered the better will be the control of the asthma attack and the quicker its resolution, reducing its possible consequences. Despite of the quick relief of the symptoms this therapy has the disadvantage of only promoting a temporary relief [8, 79]. In Table 2 is presented a list of the more common drugs used in the relief therapy of asthma attacks.

The more commonly used drugs in relief therapy are short-acting β2-selective adrenergic agonists which present similar side effects as the long-acting β2-selective adrenergic agonists [8].

Inhaled anticholinergic drugs block cholinergic response in the bronchial smooth muscle and are used as an alternative to short-acting β2-selective adrenergic agonists and like other inhaled drugs present as side effects dry mouth and unpleasant taste [8, 80].

The methylxanthine aminophylline is used in severe asthma attacks, usually only in the hospital [1]. At last, the corticosteroids used as control therapy can also be used as relief therapy but it takes more time to have effect than other drugs used specifically as relief therapy [8].

Asthma control

According to GINA [8], asthma control objective is to reach and maintain symptoms control, normal levels of activity including the practice of physical exercise, keeping pulmonary function as normal as possible, prevent asthma exacerbations, avoid side effects from therapy and prevent the mortality.

The intervention strategy established to control asthma encompasses three steps: assessment of the control, treatment to reach control and monitoring to maintain control of the disease. Based on today’s knowledge on asthma, GINA proposes a scheme, showed in Table 3, that allows to assess asthma control [8].

Although it has not been implemented any evaluation scheme of asthma control several questionnaires have been proposed. Based on the proposed evaluation in Table 3, these questionnaires allow the patient to know his degree of control of his own disease [8]. Nowadays, asthma treatment is established by degrees with the level of control of the disease determining which degree of the disease the patient belongs. Table 4 represents several therapeutic options that are recommended in each degree of severity of the disease though there are other possible therapeutic combinations, depending on the patient [77].

Generally, when the patient doesn’t have his disease controlled, treatment should move to an immediate superior step. If the disease is partially controlled, changes in therapy must be considered with an increase in the dose or adding a drug. Instead, if the disease is controlled during a period superior to 3 months the treatment can move down one step [8].

However, the proposed therapeutic options do not take into account special situations like exercise-induced bronchoconstriction or asthma exacerbations. Exercise-induced bronchoconstriction may be a sign of the need to move up one step in control therapy. Still, in patients with a controlled disease it can be made preventive therapy which includes an inhaled short-acting β2-selective adrenergic agonist. As an alternative it can be used a leu-
Asthma exacerbations must be treated as soon as possible preventing a progressive deterioration of the clinical status of the patient. As key measures it is recognized the use of inhaled short-acting β2-selective adrenergic agonists and oral corticosteroids in the exacerbation onset, reducing the inflammatory and accelerating patient recovery. Depending on the gravity of the exacerbation, which can be evaluated by the criteria detailed in Table 5, the patient can require hospitalization, during which must be carried out a detailed evaluation of respiratory function and, in case of hypoxia, oxygen must be administered [8, 85]. Once the control of the symptoms is achieved, this disease requires constant monitoring in which the patient must intervene actively. This step in asthma control involves the assessment of the symptoms and also of the respiratory function [8, 85]. The respiratory function assessment with the peak flow meter or if possible the spirometer is important in the evaluation of the patient’s response to the previously established therapy and in the adjustment of the therapy. Generally, a peak expiratory flow stabilized above 80% of the theoretical or best value indicates a good control of asthma [8, 85]. This monitoring of respiratory function performed on a day-to-day basis by the patient is crucial to identify exacerbations even before the onset of the symptoms. Small variations of the peak expiratory flow, namely a reduction to less than 80% of the theoretical or best value, indicate the onset of an exacerbation, allowing patients to act early with bronchodilator and anti-inflammatory therapy [8, 85].

Prevention

Prevention consists of the evasion of factors that can induce asthma exacerbations. The implemented measures must allow avoiding as much as possible the contact with triggers as house dust mites, animal hair, pollens, inner fungi, sudden changes in temperature, pollution and tobacco smoke, assuming the pharmacist a crucial role in smoking cessation. Effective prevention allows avoiding symptoms and exacerbations as well as changes in therapy [1, 8, 17, 85-88]. As general evasion measures the patients must ventilate the house properly and clean it often, change bed sheets frequently, avoid areas of dense vegetation, keep animals away from the house and reduce moisture from the house.

Asthma patient education

An important role of the pharmacist is to educate the asthma patient, this being the key to a successful therapeutic approach to asthma. The methods used should be tailored to each patient. It is necessary that the pharmacist explains the patient that asthma is a chronic disease not curable but manageable. It is a disease that progresses by periods of exacerbations interspersed by periods of calm and that in these periods the patient cannot neglect the therapy. In this sense the pharmacist has a duty to intervene socially to ensure the asthma patient all the information about the disease, on education and control of his own disease, on the prevention and acute treatment, including pharmacological and nonpharmacological measures [85]. For the information to be transmitted correctly is also necessary to improve and adjust the levels of communication between the patient and the health professional so the transmitted information is received by the patient and to stimulate the patient to accept his own responsibility in the control of the disease improving the quality of life and living in a active and productive way. The verbal communication between the patient and the health professional should be as clear as possible with simple and understandable language, using if necessary written or audiovisual material [8, 85].

Based on the Good Practices Guide on Asthma 2007, the pharmacist should educate the patient towards: (1) taking medication correctly; (2) understand differences between relief therapy and control therapy; (3) avoiding trigger factors; (4) monitoring the disease recognizing symptoms and analyzing peak expiratory flow values; (5) recognizing signs of deterioration and if necessary contact the doctor [85].

About the therapy, the pharmacist plays a very important role once it is in the pharmacy that asthma patient first contacts with inhalers. Towards a correct administration of the medication, the pharmacist should explain the patient the proper use of inhalers. In this sense, it is important to know the different inhalers in the market and the pharmacist should endeavor to give the best knowledge for each type of inhaler, promoting the proper use of it. The presurized inhalers constitute the classic model of inhaler and should be used by the following method: (1) shake inhaler holding it with two fingers; (2) exhale normally and enter the mouthpiece of the device between the teeth and close the lips; (3) tilt the head back and inhale slowly and deeply while the device releases the drug by a slight pressure with a finger; (4) hold the breath as long as possible for a good retention of the drug in the lungs; (5) remove the mouthpiece and exhale slowly [89]. The technique used by the patient is crucial and there should be a perfect coordination between the pressure applied by the fingers and the inhalation to avoid waste of drug, which can be swallowed. In certain patients, performing this technique can be difficult to achieve being used a spacer, which allows to diminish the deposition of drug in oral cavity [85, 89].

As for monitoring, pharmacist should sensitize patients to the frequent measure of peak expiratory flow with a peak flow meter. Towards a good assessment of the respiratory function, the pharmacist should explain the patient how to interpret the values of peak expiratory flow comparing with the best personal value or with the theoretical value established in the intervention plan. This allows the patient to assess reductions in peak expiratory flow which might indicate the beginning of an exacerbation allowing the patient to self-assess his own disease according to the degrees in order to reach control of the disease [85]. The pharmacist counseling should appeal to patient adherence to asthma therapy and self-monitoring of the disease but also alert to the possible side-effects which one may experience, often leading the patient to quit therapy. It should be noted that adherence to treatment plan increases when the patient has the opportunity to talk about his concerns, fears and expectations related to asthma, so the pharmacist should give special attention to these patients.

Monitoring of asthma patient

Given the necessity of constant monitoring of asthma and all the care it involves and requires by the patient, the partial or total non-adhesion to treatment plan is very common. So it is extremely important that the pharmacist can monitor the patients [8, 85].

Non-adhesion to treatment plan can occur in many ways which include: failure to acquire medication by patients, incorrect dose, omission of doses, suspension of one or more drugs, non prevention of exposure to allergens and poor technique in the use of inhalers [85].

In order to assess adherence and response to therapy, the pharmacist should talk to the patient ascertaining: (1) the fulfillment of the objectives of the treatment plan, adjusting if necessary the medication and the plan itself; (2) the technique of inhalers, spacers and peak flow meter used, again demonstrating the correct technique and encouraging patient to illustrate the presence of the pharmacist; (3)
taking proper medication, considering possible changes to the treatment plan; (4) implementation of measures to eviction of triggers, explaining the measures again; (5) possible questions and concerns of the patient, which must be clarified clearly; (6) possible reasons of non-adhesion to the treatment plan.

CONCLUSION

Asthma is one of the most prevalent chronic diseases worldwide, thus being an important health problem. To a better efficacy and efficiency of healthcare to the asthma patient, the health professional should adopt the best professional practices in order to improve the quality of life and well being of the patient. Thereby, the pharmacist as a healthcare provider has as main role to develop skills that allow him to help the asthma patient in the self-monitoring of the disease. Continuous monitoring and education of asthma patient is crucial to a successful treatment and control of asthma, and the pharmacist must alert the patient to trigger factors and promote adhesion to therapy thereby contributing to the reduction of morbidity and mortality related to this disease.

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