

Prophylactic pharmacologic treatment of asthma

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Pharmacologic treatment is usually offered to all patients with bronchial asthma for occasional application or regular prophylactic treatment. The approach to the chosen pharmacologic treatment is dictated by goals of therapy and current thinking about the pathophysiologic processes leading to asthma. Inflammation in the bronchial wall with infiltration of different types of inflammatory cells, such as mononuclear cells, mast cells, and eosinophils, has been observed for many years in histologic studies from death caused by severe asthma (10, 29). In recent years an inflammatory process in the airways has also been documented in even mild cases of asthma (15). A more refined description of specific inflammatory changes diagnostic for bronchial asthma is not available, and the processes involved in the generation of bronchial inflammation are poorly understood. The exact mechanism whereby the inflammatory process may lead to the components of asthma is little understood and pharmacologic intervention in defined pathophysiologic processes and mediator reactions is currently not available for clinical use. Although not clearly defined, inflammation is regarded as a very important part of the asthmatic disease and has been incorporated in the newly proposed definition of bronchial asthma in the international asthma report (28): "Asthma is a chronic inflammatory disorder of the airways in which many cells play a role including mast cells and eosinophils. In susceptible individuals this inflammation causes symptoms which are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment and causes an associated increase in airway responsiveness to a variety of stimuli."

This definition shows that the inflammatory disorder is regarded as at least partly responsible for airway hyperresponsiveness and, consequently, for airway symptoms because of airflow obstruction (Fig. 1).

The goals of treatment

It is important to assess disease severity and adjust the components of treatment accordingly. The treatment goals must be easy to obtain and possible to evaluate by any physician. In practice, treatment of bronchial asthma should aim for the following:

- 1) a normal or as near normal a lung function as possible
- 2) prevention of asthma exacerbations and asthma attacks during both day and night, including noc-

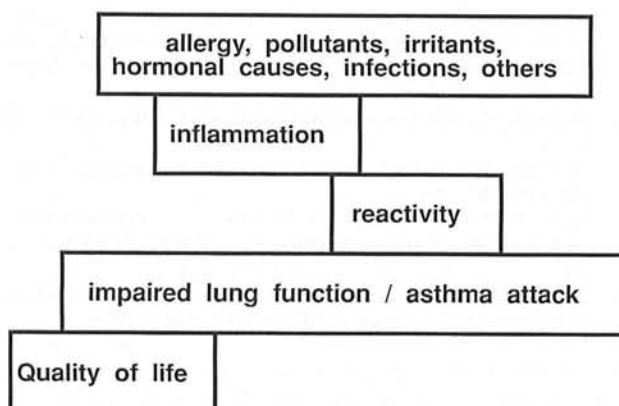


Fig. 1. The theoretic pathogenetic mechanisms in bronchial asthma and their suggested associations.

tural asthma, exercise-induced asthma, or asthma induced by inhalants or allergens

3) Prevention of deterioration with development of irreversible airways obstruction.

Ideally, the treatment goals should be obtained without causing side-effects or limitation in the patient's ability to lead a normal life. Treatment that can fulfill treatment goals must be regarded as effective prophylactic intervention.

Assessment of asthma severity

Asthma severity and disease activity can be classified according to the components in the definition of asthma. Usually, lung function parameters and clinical symptoms are used in the assessment of severity. However, the appreciation that mild symptoms can represent serious alteration in the airways should be more widely accepted and understood. Even patients with seemingly mild symptoms may have obvious macroscopic abnormalities in their airways and also marked changes in histology (9). The proposed classification of asthma severity according to clinical features (28) (Table 1) is a good working model for daily clinical use, but we still have limited information about the associations between bronchial inflammation, bronchial hyperresponsiveness, clinical symptoms (4, 19), and long-term outcome.

It is possible that the chronic inflammatory processes in the airways associated with asthma have elements that may lead to irreversible structural changes (26), causing an accelerated fall in lung function in asthmatics (31). It is, however, not known whether there are protective elements present in the inflammatory reaction which may have beneficial as-

pects. Suppression of inflammation may, in other words, be a two-edged sword, and we do not know how to balance our intervention.

Inhaled corticosteroids as first-line treatment

Asthma is traditionally regarded as a chronic disease with periods of exacerbation and remission. As no cure exists for asthma, it is important to keep the patient as close as possible to treatment goals and gain a long-lasting remission.

Inhaled corticosteroids are well documented in the prophylactic treatment of bronchial asthma of all severities and are the most effective and reliable suppressors of inflammation. The exact mechanism of corticosteroid action is not known, but the result of corticosteroid treatment is an amelioration of the inflammatory cell infiltrate (22). This influence on asthmatic bronchi is regarded as the reason for the observed clinical benefits. Regular treatment with inhaled corticosteroids reduces bronchial hyperresponsiveness to both specific and nonspecific bronchoconstrictors (42); that is, it reduces the bronchoconstriction in sensitive subjects following allergen inhalation as well as in reactions following exercise or inhalation of irritants. Clinically, the antiasthma effect is manifested in a reduction of asthma exacerbations (35), of the diurnal variation in lung function (6), and of daily symptoms.

The onset of corticosteroid action varies according to the parameter tested for and in longer-term studies improvements occur even after 2–3 months of treatment (44). This probably points towards a treatment strategy with a more aggressive initial

Table 1. Classification of asthma severity* (from National Heart, Lung, and Blood Institute, 1992)

Asthma severity	Clinical features before treatment	Lung function	Regular medication usually required to maintain control
Mild	● Intermittent, brief symptoms <1–2 times a week ● Nocturnal asthma symptoms <2 times a month ● Asymptomatic between exacerbations	● PEF** >80% predicted at base line ● PEF variability <20% ● PEF normal after bronchodilator	● Intermittent, inhaled, short-acting beta₂-agonist (taken as needed) only
Moderate	● Exacerbations >1–2 times a week ● Nocturnal asthma symptoms >2 times a month ● Symptoms requiring inhaled beta₂-agonist almost daily	● PEF 60–80% predicted at base line ● PEF variability 20–30% ● PEF normal after bronchodilator	● Daily inhaled anti-inflammatory agent ● Possibly a daily, long-acting bronchodilator, especially for nocturnal symptoms
Severe	● Frequent exacerbations ● Continuous symptoms ● Frequent nocturnal asthma symptoms ● Physical activities limited by asthma ● Hospitalization for asthma in previous year† ● Previous life-threatening exacerbation†	● PEF <60% predicted at base line ● PEF variability >30% ● PEF below normal despite optimal therapy	● Daily inhaled anti-inflammatory agent at high doses ● Daily, long-acting bronchodilator, especially for nocturnal symptoms ● Frequent use of systemic corticosteroids

* The characteristics noted in this table are general, and they may overlap because asthma is highly variable. Furthermore, an individual's classification may change over time. One or more features may be present to be assigned a grade of severity. An individual should usually be assigned to the most severe grade in which any feature occurs. Once the minimum medication required to maintain control of asthma has been identified, this medication requirement reflects the overall severity of the condition.

** Forced expiratory flow.

† The potential severity – related to a patient's past history (for example, a previous life-threatening exacerbation or a hospitalization for asthma in the previous year) as well as present status – should be considered at all times.

treatment with inhaled corticosteroids, and, when sufficient symptom control has been obtained, a gradual reduction in daily dosage until the minimal dosage controlling asthma is reached.

However, the problem is how to determine when the maximum benefit of the steroid effect has been reached, and research is necessary to define which treatment goal should be used as the standard asthma control.

To achieve long-term treatment goals, we must be able to define the key components leading to airways damage, and this is not possible today. This immediately raises the question of what an inhaled corticosteroid can maximally achieve in the individual asthmatic patient. The asthmatic population is not homogeneous and includes some patients fully steroid sensitive and responsive, and, at the other extreme, patients totally resistant to corticosteroids. It is anticipated that, depending on sex, age, smoking history, occupational history, etc., patients may fall between the two extremes and be partly responsive to corticosteroids (Fig. 2).

As for other treatments, we must remember that the dose-response characteristics of corticosteroids are similar to those of most other pharmacologic treatments; that is, that linearity exists between the log dose and the effect (18). This, on the other hand, implies that relatively more benefit is gained from the initial dosages, and proportionally larger doses must be given to obtain a certain additional treatment effect (Fig. 3). The onset and maximum obtainable effect vary in corticosteroid-sensitive subjects (Fig. 3), making clinical assessment of effect a matter of individual judgment.

The topically active corticosteroids, such as beclomethasone dipropionate and budesonide, have proved to be both safe and effective in long-term clinical use in lower and moderately high dosages. In daily dosages around 1 mg, signs of an influence on biochemical parameters begin to appear, although

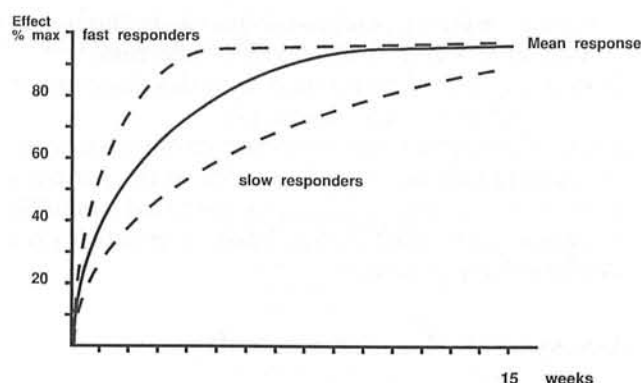


Fig. 3. The dose-response characteristics of corticosteroids.

the clinical relevance is not known (17). The changes are indications of systemic absorption. It is possible that individual factors play a role, and the metabolism of different corticosteroids may vary between patients and alter the impact of systemic reactions to a particular drug (33).

The considerations concerning the safety of long-term treatment with inhaled corticosteroids have resulted in a recommendation that about 1 mg inhaled corticosteroid daily for long-term treatment in adults and half that dose or less in children can be regarded as safe (28). Above this dose, inhaled corticosteroid may be supplemented with sustained release theophylline, oral β_2 -agonist, or a long-acting, inhaled β_2 -agonist. Individual assessment of the appropriate corticosteroid dose for long-term treatment must be taken on clinical grounds today, but it is hoped that measurements of inflammatory markers in serum or sputum can be developed. Asthma must not be regarded as a disease of corticosteroid lack, and the lack of a clinical response to corticosteroid does not exclude a diagnosis of asthma.

Sodium cromoglycate and nedocromil sodium

The cromones are prophylactic drugs for inhaled use that inhibit the development of mucosal inflammation but seem unable to eliminate or reduce existing inflammatory changes. This observation is mainly based on clinical experimental studies (5, 7, 27). No formal studies have shown the influence of sodium cromoglycate or nedocromil sodium on inflammatory changes in bronchial biopsies from asthmatics. In comparative studies with clinical end points, recommended doses of sodium cromoglycate and nedocromil sodium have been equivalent to about 400 μ g of inhaled corticosteroid daily (1, 37). The drugs have been used as an alternative to low-dose corticosteroids (28). This does not mean that the

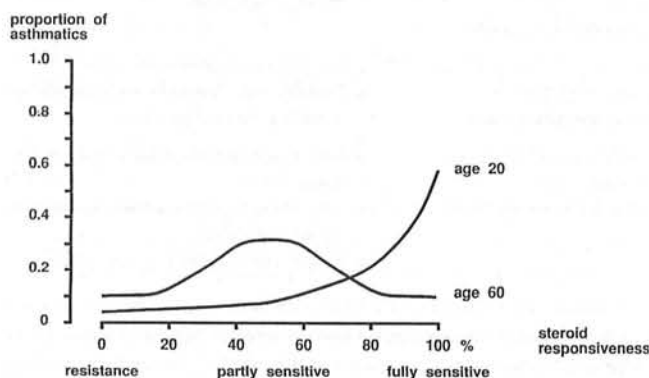


Fig. 2. Schematic presentation of the theoretic distribution of asthmatic patients according to the corticosteroid-sensitive part of their bronchial asthma.

drugs are interchangeable or have similar influence on bronchial pathophysiology and long-term outcome.

Bronchodilators

We cannot evaluate the clinical significance of experimentally proved effects such as those on vascular permeability, gland secretion, ciliary beat frequency, diaphragmatic strength, etc. Oral bronchodilators such as β_2 -agonists and methylxanthines can produce bronchodilation, but their influence on bronchial reactivity is questionable and of little clinical importance (25). At equivalent bronchodilation, more side-effects are caused by oral preparations than by inhaled β_2 -agonists (23), and the inhaled form of application reduces bronchial reactivity extremely well (12). The new, long-acting β_2 -agonist for inhaled use maintains the influence as bronchodilator and antireactive agent for 12 h in most patients (30, 40). No tachyphylaxis to the bronchodilatory activity seems to develop even after a long-term use (39). In comparative studies, inhaled, long-acting β_2 -agonists have shown better clinical efficacy, as compared with regular inhalation of a short-acting β_2 -agonist four times daily (3).

It is possible that inhaled, long-acting β_2 -agonists can influence processes leading to inflammatory events in the bronchi, whereas they seem to have no influence on chronic inflammatory changes. Inhaled, long-acting β_2 -agonists inhibit the early- as well as the late-phase, allergen-induced bronchial reaction and postchallenge increase in nonspecific bronchial hyperresponsiveness (38). In a recent study regular treatment with an inhaled, long-acting β_2 -agonist resulted in a reduction of macroscopic signs of bronchial inflammation (8).

Much controversy exists concerning the safety of regular treatment with inhaled β_2 -agonists (13, 36), but the issue has not been settled by carefully controlled clinical trials (3). Regular treatment with oral β_2 -agonists was many years ago shown to improve asthma control and reduce the need for oral corticosteroids (11). Regular use of inhaled β_2 -agonists, short-acting as well as long-acting, has been associated with improved asthma control (24, 41). This seems especially evident for the newly introduced, long-acting β_2 -agonist for inhaled use. Stopping the regular use of inhaled β_2 -agonist has in some studies been associated with a small increase in bronchial sensitivity to histamine or methacholine (20, 21), but the clinical significance is unknown. In other studies, decreases in bronchial reactivity were found with comparable protocols (32, 34). Unnecessary scepticism as well as overreliance on any treatment can prove detrimental and deprive

asthmatics of treatment possibilities and optimum asthma control. The anticholinergic drugs ipratropium and oxitropium bromide are bronchodilators but have little influence on bronchial hyperreactivity (14). In chronic asthma treatment, their place has not been established, but they may be recommended as an alternative for patients with side-effects from other bronchodilators.

Practical considerations

The practical application of standard treatment recommendations faces many obstacles in daily clinical life. The acceptance by patients and doctors of the asthma diagnosis is necessary, and the need to comply with regular prophylactic treatments is obvious. The inconveniences of long-term treatment are not only psychological but also economic. Although it is difficult to value health, effort should be devoted to elucidating the cost-effectiveness of recommended treatments and finding a way to evaluate an improved quality of life. Drug costs are influenced by many factors including development cost, patent length, and distributor costs. Efforts are currently being made to reduce the costs of medication by influencing the forces driving the market price.

The impact of bronchial asthma on society and the individual patient is increasingly acknowledged in the Western world, partly because of the frightening increase in asthma incidence during the last 50 years. The concern has led to a better understanding of the asthmatic disease process, and this, in turn, has led to the generation of consensus reports with recommendations of treatment modalities (2, 16, 28, 43).

All reports recommend the administration of inhaled corticosteroids when lung function is chronically reduced, even slightly, or if inhaled bronchodilators are needed more than twice a week. The initial dosage of corticosteroid should be chosen so as to gain control of asthma symptoms and disease processes as fast as possible. A high initial dose is recommended, and it is gradually reduced to a maintenance level. If the treatment goals are not fully achieved by inhaled corticosteroids, regular prophylactic treatment with bronchodilators, preferably inhaled, long-acting β_2 -agonists, is recommended. This is a simple and flexible treatment of extreme efficacy in most patients. The dose of inhaled corticosteroid given for long-term use must be individually chosen, considering therapeutic benefits and side-effects. It is important to motivate patients through education in disease mechanisms and treatment possibilities, regular follow-up, and the adoption of a great degree of self-care.

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