How to Use Anti-Allergy Drugs

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Abstract: Currently, anti-allergy drugs are classified, on the basis of their action mechanism, into 5 types including mediator-release inhibitors, histamine H₁ antagonists, thromboxane A₂ inhibitors, leukotriene antagonists, and Th2 cytokine inhibitors. The asthma treatment guideline released in Japan stipulates treatment with one of these types of anti-allergy drugs, regardless of the severity of disease. There are no definite grounds for the choice of anti-allergy drugs. When the patient has complications involving other allergic diseases, the physician chooses, in order of preference, histamine H₁ antagonists, mediator-release inhibitors, and Th2 cytokine inhibitors, depending on the indications with the concomitant allergic disease. When symptoms are severe, leukotriene antagonists and thromboxane A₂ inhibitors are chosen. The physician may also consider increased doses of steroid inhalants and sustained release theophylline. At present, the use of two or more anti-allergy drugs together is not acknowledged, but this will be the subject of research in the future, because anti-allergy drugs with different mechanisms of action used at the same time will theoretically increase their effects.

Key words: Mediator-release inhibitors; Histamine H₁ antagonists; Thromboxane A₂ inhibitors; Leukotriene antagonists; Th2 cytokine inhibitors

Introduction

Bronchial asthma is an obstructive respiratory disease characterized by reversible occlusion, hypersensitivity, and chronic inflammation of the airway. Allergic reactions play an important role as a factor in inducing airway inflammation. When asthma patients are tested for allergies, using a skin reaction test, about 70% exhibit the presence of IgE antibodies by showing positive reactions to house dust and its major component, the house dust mite (dermatophagoides). About 70% of these patients had diseases involving atopic conditions. The test results revealed that allergic reactions can be considered an important target of asthma treatment.

What Are Anti-allergy Drugs?

“Anti-allergy drug” is the general term for drugs that regulate the release and action of...
chemical mediators involved in allergic reaction, mediated by IgE (immediate or type I allergic reaction), or inflammatory mediators (Table 1). The many anti-allergy drugs currently on the market are classified, on the basis of their action mechanism, into 5 types including mediator-release inhibitors, histamine H₁ antagonists, thromboxane A₂ inhibitors, leukotriene antagonists, and Th2 cytokine inhibitors.

Types of Anti-allergy Drugs (Table 2)

1. Mediator-release inhibitors

Mediator-release inhibitors include DSCG (sodium cromoglicate), which was the first anti-allergy drug developed. These drugs are expected to be effective in 30 to 40% of mild to moderate cases with atopic asthma, but it takes them 4 to 6 weeks to manifest any effect. As these drugs do not have anti-histamin action, they do not induce drowsiness in patients.

2. Histamine H₁ antagonists

Histamine H₁ antagonists more or less induce drowsiness, which generally remits or disappears within several days after the start of treatment. Histamine H₁ antagonists also inhibit mediator release and are effective in 20 to 30% of mild to moderate cases with atopic asthma, but it takes them 4 to 6 weeks to manifest...
any effect.

3. Thromboxane A₂ inhibitors and antagonists

Thromboxane A₂ inhibitors consist of 2 types of agents, i.e., thromboxane A₂ synthetase inhibitors and thromboxane A₂ antagonists (receptor antagonists).

These drugs are effective in 40% of mild to moderate atopic and mixed-type asthma. Since their effects can be observed in only 2 to 4 weeks of treatment, it is possible to assess results at an earlier stage than with mediator-release inhibitors and histamine H₁ antagonists, which must be administered for 4 to 6 weeks before any effect can be observed.³,⁴)

These drugs are also reported to be effective against infectious asthma. However, due to a case of severe hepatic disorder reported after marketing, physicians are recommended to administer the thromboxane A₂ antagonist, seratrodast, and conduct monthly hepatic function tests.

4. Leukotriene antagonists

LTC₄, D₄ and E₄ receptor antagonists are available for use as leukotriene antagonists. Much attention has been focused on these drugs in Europe and the U.S., where two drugs were developed, but Japan took the lead and developed pranlukast hydrate, which has been valuated highly since it went on the market.

These drugs are effective in 50 to 60% of mild to moderate atopic and mixed-type asthma. Since the effects of the drug appear in only several days to 1 week, or 2 to 4 weeks at the latest, results can be assessed much sooner than with mediator-release inhibitors and histamine H₁ antagonists, which must be administered for 4 to 6 weeks before any effects can be observed.⁵ Another report⁶ found that these drugs not only inhibited airway inflammation but also inhibited airway hypersensitivity in asthma patients. Moreover, aspirin- and exercise-induced asthma is expected to be inhibited with these drugs since they showed inhibitory effects in both a salpyrine inhalation and an exercise-induced asthma tests.

Zafirlucast and Montelukast, developed in the West, have recently been put on the market in Japan.

5. Th2 cytokine inhibitors

Th2 cytokine inhibitors inhibit the production of excessive production of Th2 cytokines that induce the IgE antibodies and allergic inflammation. Among Th2 cytokines (Table 3), IL-4, which is involved in the production of the IgE antibody, and IL-5, which is involved in the activation of eosinophil, have been attracting particular attention. Reports have also found that IL-5 production is enhanced in asthma patients, regardless of any allergic conditions, suggesting that Th2 cells are generally predominant in asthma.

Currently, the only drug available in this category is suplatast tosilate, which was developed in Japan. This drug inhibits the production of IL-4 and IL-5 and is reported to inhibit both eosinophil infiltration in the airway mucosa and airway hypersensitivity.⁷) However, the drug has to be administered for 6 to 8 weeks.
before any effect can be observed, and its effects are manifested slowly. In view of the pathology of asthma, more attention should be paid to the development of Th2 cytokine inhibitors.

**Positioning Anti-allergy Drugs in Asthma Treatment Guidelines**

This section describes how the above-mentioned anti-allergy drugs are positioned in asthma treatment guidelines, according to the “Asthma Prevention and Control Guidelines” (prepared in 1998 by the Immunity & Allergy Research Group of Ministry of Health & Welfare in Japan; revised in 2000). Anti-asthma drugs are classified into those that act against asthma attacks, or relievers which remove asthma symptoms, and those for long-term control, or controllers which alleviate inflammation and stabilize the patient’s condition. Obviously, anti-allergy drugs are classified as the controllers (Table 2).

According to the guidelines, asthma is classified into 4 steps of severity, i.e., mild intermittent, mild persistent, moderate persistent, and severe persistent. The guidelines recommend the continuous or persistent use of anti-allergy drugs in treating each of these steps (refer to appendix, page 368).

1. **Step 1**
   Step 1 severity consists of the onset of asthmatic symptoms such as cough and respiratory difficulty once or twice a week. At this stage, physicians may consider using any of the anti-allergy drugs, excluding DSCG (sodium cromoglicate), and the positioning of anti-allergy drugs is similar to that of low-dose inhalant steroids. Use of β2 stimulants and theophylline for controlling the symptoms as well as DSCG inhalation before exercise and exposure to allergens is recommended at this step.

2. **Step 2**
   Step 2 severity consists of the onset of the above symptoms two or more times a week. At this step, the guidelines recommend the continuous use of any of the anti-allergy drugs, in addition to the continuous use of low-dose inhalant steroids (beclomethasone dipropionate; BDP 200–400μg/day, fluticasone propionate; FP 100–200μg/day) and sustained-release theophylline.

3. **Step 3**
   Step 3 severity consists of the presence of chronic symptoms. At this step, the guidelines recommend the continuous use of leukotriene antagonists/thromboxane A2 inhibitors in addition to the continuous use of middle-dose inhalant steroids (BDP 400–800μg/day, FP 200–400μg/day), sustained-release theophylline, and patch/oral/inhalant β2 stimulants.

4. **Step 4**
   Step 4 severity consists of not only very severe and persistent but also aggravated symptoms. At this step, the guidelines suggest the intermittent use of oral steroids and the continuous use of leukotriene antagonists/thromboxane A2 inhibitors in addition to the continuous use of high dose inhalant steroids (BDP 800–1,600μg/day, FP 400–800μg/day), sustained-release theophylline, and patch/oral/inhalant β2 stimulants.

The continuous use of anti-allergy drugs is suggested rather than recommended in Step 1 and Step 4 because their usefulness has not yet been fully proven. However, it has already been reported that these drugs could reduce the use of high-dose inhalant steroids.

**Personal Views on the Administration of Anti-allergy Drugs**

As described above, anti-allergy drugs are positioned for long-term control of asthma and are selected according to the severity of the patient’s condition. This leads to various questions about the administration methods of these drugs.
The usefulness of anti-allergy drugs at Step 1 has yet to be established. In other words, the guidelines will recommend aggressive treatments with these drugs if they are proven to be effective as a part of an early intervention against asthma. At this moment the author generally starts administering anti-allergy drugs to patients at Step 2 or higher.

I will prescribe anti-allergy drugs with antihistamin action if the patient has complications involving other allergic diseases such as allergic rhinitis and atopic dermatitis, even if the asthma itself is mild. Since leukotriene antagonists have recently been demonstrated to be effective on nasal occlusion attributable to allergic rhinitis, treatment with this type of drug should be taken into consideration, depending on the patient’s symptoms. Based on their pharmacological action and therapeutic effects, it is all together conceivable that we will include leukotriene antagonists among the first drugs of choice used at Step 1.

For the treatment of the patient at Step 2 I start with a low-dose inhalant steroid and sustained-release theophylline. Additional anti-allergy drugs will be administered if the patient’s symptoms are not controlled with satisfaction. There are no definite criteria for selection. When the patient has additional allergic diseases, drugs are chosen according to the presence or absence of contraindications against that disease. In such cases, physicians may choose from mediator-release inhibitors, histamine H₁ antagonists or Th2 cytokine inhibitors.

Caution must be exercised and it is not always possible to administer histamine H₁ antagonists, as they may induce drowsiness in some patients. Since the efficacy rate of mediator-release inhibitors is rather low, treatment with Th2 cytokine inhibitors should be attempted if no effect is observed in 4 to 6 weeks with mediator-release inhibitors. If both types of drugs are ineffective, I will consider administration of leukotriene antagonists as well as increase of doses of inhalant steroids and sustained release theophylline.

When the condition of a patient corresponds to Step 3 or 4, I administer a leukotriene antagonist first. If ineffective, I will administer thromboxane A₂ inhibitors. What is especially important in the treatment of patients at Steps 3 and 4 is adding a concomitant drug while prescribing each drug at a satisfactory dose, within the safe range. This is expected to enhance the actions of leukotriene antagonists and thromboxane A₂ inhibitors.

Though leukotriene antagonists and thromboxane A₂ inhibitors are similarly classified as anti-allergy drugs, mechanisms of their action are distinct. Concomitant administration of these drugs is not allowed at present, but concomitant use of anti-allergy drugs with different mechanisms of action is theoretically expected to increase their effectiveness. In this regard, we should investigate if the concomitant administration of these drugs is beneficial.

**Future Prospects for Anti-allergy Drugs**

Due to their slow action and rather low efficacy rate, the development of anti-allergy drugs was criticized at the initial stage. Thanks to earnest support and efforts, researchers in Japan were able to develop the first leukotriene antagonist and the first thromboxane A₂ inhibitor and antagonist. I strongly hope that a highly specific anti-allergy drug will be developed to improve asthma treatment in the future. When it becomes possible to predict the efficacy of a drug at the genetic level, it will become possible to perform so-called “tailor-made medicine.”

**REFERENCES**


