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Clinical Evaluation of Antiallergic Agents

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Abstract □ Testing methods used to detect antiallergic activity are described for several pharmacological classes of drugs. The pharmacodynamics of each drug determine the type of testing required to detect antiallergic or antiasthmatic activity.

Keyphrases □ Pharmacokinetics—clinical testing in mildly asthmatic human volunteers, dose–response curve of antiallergic drugs □ Antiallergic drugs—pharmacokinetics, various clinical testing procedures in humans, inhibition of mediator release, cyclic adenosine monophosphate levels, potential asthma inhibitors □ β-Adrenoceptor agonists—antiallergic drug testing, bronchiolar smooth muscle, cyclic adenosine monophosphate levels, effects on mediator release □ Asthma—review of current theories, clinical evaluation, symposium, antiallergic drugs

Hypersensitivity involves an allergic reaction that is an immunological event characterized by the release of a chemical mediator, histamine or slow-reacting substance of anaphylaxis, in response to exposure to a foreign antigen. Foreign (environmental) antigens are usually complex protein mixtures such as cat dander or ragweed pollen. Initial antigen exposure results in the elaboration of antibody of the immunoglobulin E class, which, as circulating specific immunoglobulin E antibody, is in equilibrium with cell-fixed immunoglobulin E on circulating basophils or tissue mast cells. When a subsequent environmental antigenic insult occurs, the antigen combines with the cell-fixed immunoglobulin E antibody, whereupon histamine and other chemical mediators are released to act directly on target tissue. Accordingly, the characteristic allergic reactions seen in asthma, rhinitis, urticaria, and even systemic anaphylaxis reflect the anatomic sites where histamine and other chemical mediators are released as well as their respective tissue responses.

DISCUSSION

Histamine release induced by antigen can be modified by drugs that act on various stages within the release mechanism. For example, the β-agonists, isoproterenol, ephedrine, metaproterenol, and terbutaline, activate adenyl cyclase to increase intracellular levels of cyclic adenosine monophosphate, an enhancement that prevents histamine release. Because phosphodiesterase catalyzes the conversion of cyclic adenosine monophosphate to 5′-adenosine monophosphate, inhibition of this enzyme by drugs such as the xanthines (theophylline) arrests the breakdown of cyclic adenosine monophosphate, thereby preventing histamine release.

Cromolyn sodium is the prototype of a new class of compounds that act presumably by preventing mediator release, although the exact mechanism of action is unknown. The anti-inflammatory steroids appear to stabilize the mast cell membrane and also enhance β-receptor sensitivity. The prostaglandins not only influence intracellular cyclic adenosine monophosphate but also may prevent mediator release, whereas prostaglandin synthetase inhibitors may regulate allergic hypersensitivity reactions in either direction. At the cellular level, α-agonists (phenylephrine) and cholinergic agonists (acetylcholine) may increase intracellular cyclic guanosine monophosphate by stimulating guanyl cyclase and enhancing histamine release. On the basis of experimental evidence, α-blockers and cholinergic antagonists may have some usefulness as antiallergic agents.

The classical antihistamines, exemplified by diphenhydramine, compete with histamine at H_1-receptor sites to allay allergic reactions. This group has a new member with different pharmacological attributes, the H_2-receptor antagonist cimetidine, which blocks gastric acid secretion. Although this kind of blockade has not previously been associated with allergy treatment, preliminary studies suggest that H_1- and H_2-blockers in combination may be effective against urticaria (1–3). Drugs that alter the immune response also may be considered antiallergic. Ragweed extract or denatured antigens can raise the protective immunoglobulin G antibody titers and reduce the severity of an allergic reaction.

A number of clinical testing procedures can be used to evaluate new antiallergic medications. The inhalation challenge method elicits an asthmatic attack under laboratory conditions, enabling a test drug to be evaluated (4). In this technique, mildly asthmatic volunteers with near normal pulmonary function inhale graded doses of antagonists such as antigen, methacholine, or histamine, using a specialized inhalation dosing apparatus, the inhalation dosimeter. Spirometry and specific airway conductance are monitored, and the dose–response curves to the inhaled antagonists indicate patient sensitivity.

The provocation dose, defined as the amount of antagonist causing a 20% fall in forced expiratory volume in 1 sec, is interpolated from the dose–response curve and used as a reproducible index of patient sensitivity to the inhalant.

A change in the dose–response curve or a shift of the provocation dose toward a higher antigen requirement indicates an alteration of antigen sensitivity. By this procedure, antiasthma agents can be evaluated for

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relative efficacy and compared pharmacokinetically. Also, the premedication interval can be lengthened to provide information relative to the duration of the blocking activity after the administration of the protective dose of the test drug.

Isoproterenol kinetics have been studied with this procedure. When premedication with isoproterenol was accomplished 1 hr before antigen provocation, the sympathomimetic agent was effective as a bronchodilator but did not act long enough to inhibit the response to inhaled antigen 1 hr later. When isoproterenol was given every 0.5 hr in conjunction with inhaled antigen, the dose–response curve shifted significantly in the direction of increased antigen requirement. However, when isoproterenol was admixed with the antigen and given simultaneously, complete inhibition of the antigen response occurred. These observations correlate well with *in vitro* studies, which revealed that a peak accumulation of cyclic adenosine monophosphate occurred within 5 min of exposure to isoproterenol, as did a concomitant inhibition of antigen-induced histamine release (5).

Similar studies with selective adrenergic agonists have shed light on the pharmacology involved in the bronchomotor response. Phenylephrine, primarily an α-agonist, elicits bronchodilator responses and inhibits inhaled antigen effects in the manner of isoproterenol, a β-agonist, although less effectively. This observation refutes the popular belief that α-adrenergic receptors of bronchiolar smooth muscle cause bronchospasm when activated. On the contrary, the evidence suggests that there are few, if any, α-receptors in bronchiolar smooth muscle and that any activity caused by α-agonistic drugs is due to the unopposed weak β-specificity (6).

Bronchial provocation techniques have been used extensively to study the physiology of asthma and the pharmacology of antiallergic drugs. β-Agonists, xanthines, anticholinergics, prostaglandins, and the cromolyn-type inhibitors have all been evaluated by these methods. The most effective agents in preventing bronchospasm by inhalation are the β-adrenergic agonists. Isoproterenol is the most effective drug in this respect when given simultaneously with the antigen. Metaproterenol and terbutaline, the latter not yet approved for inhalation, have a longer duration (7).

Anticholinergic drugs, including atropine, are not yet available for inhalation in the United States, although they have been evaluated in bronchoprovocation studies. Atropine causes considerable baseline elevation and is a bronchodilator that diminishes the resting bronchial vagal tone (8). Irritant-induced bronchospasm caused by inhalation of dust or cold air is mediated by the vagus nerve, a cholinergic pathway, whose responses are effectively blocked by inhaled atropine (9). Antihistamines (H_1-blockers) are ineffective when inhaled before antigen challenge, suggesting that mediators other than histamine may be involved in allergic bronchospasm. The synthetic prostaglandins, while not yet in the clinical testing stage, represent another class of potential asthma inhibitors.

The exercise challenge is more physiological or "natural" than the inhalation challenge. Exercise protocols require the performance of pulmonary function tests after a suitable patient jogs on a treadmill for 6–8 min. Following this exercise, susceptible patients usually have a significant fall in their pulmonary function. A test drug can be introduced before the exercise challenge, and its inhibitory capabilities can be studied. This procedure seems best suited for evaluation of the cromolyn-type agents. Atropine, while raising the baseline, does not usually prevent the relative drop in pulmonary function that occurs after exercise (10, 11). Some protection is afforded by this anticholinergic, however, because of the elevated baseline pulmonary functions. The β-adrenergic agonists, isoproterenol and terbutaline, are quite effective through mechanisms of baseline elevation as well as prevention of the exercise response (7). On the other hand, inhaled antihistamines are ineffective against exercise challenge, although they possess varying degrees of anticholinergic activity (8).

The most widely employed experimental method of drug evaluation is the maintenance of a symptom diary often supplemented with routine pulmonary function tests. Diaries that measure chronic symptoms of wheezing, shortness of breath, chest tightness, and cough and that assign a score for intensity and duration are quite useful, especially when medication use and pulmonary function are integrated into the diary. Such diaries are also effective for monitoring the effects of immunotherapy (allergy shots) for the treatment of seasonal hay fever (12).

In summary, drugs representative of many pharmacological categories are useful in the treatment of asthma and other allergic illnesses. An understanding of their pharmacodynamics is critical to the design of appropriate clinical trials as well as to proper prescribing. When underlying mechanisms are not understood or are unclear, empiricism may be necessary for drug evaluation. As the mechanisms underlying the asthmatic state become better known, the potential for optimal therapy will emerge.

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