Drug Treatment of Disease

THE ANTIHISTAMINE COMPOUNDS

BY

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An illuminating approach to the action of antihistamine compounds can be made by looking at them from the point of view of the pharmaceutical manufacturer. When a compound with new properties is introduced which are likely to command for it a wide use in medicine, each pharmaceutical firm is anxious to introduce a different compound with the same properties for the manufacture of which it will have the sole rights. Many compounds are prepared and tested first by laboratory methods and then clinically, but it is often difficult to make a final appraisal of the value of any substance until after it has been launched on the market.

The first antihistamine was mepyramine maleate ("neo-antergan"), and it has been sold in Great Britain under the trade name "anthisan." The aim of other manufacturers was therefore either to introduce a compound of a quite different formula with the same properties or to introduce a similar compound with a modified formula. As examples of a similar compound with a modified formula we may take tripeleennamine ("pyribenzamine"), methapyrilene ("histadyl"), halopyramine ("synopen"), and also chlorpheniramine maleate ("piriton"), all of which are very close chemically to anthisan. Diphenhydramine, or "benadryl," differs considerably from anthisan, though both contain the grouping dimethylaminoethyl. Substances chemically close to benadryl are bromazine ("ambodryl") and diphenylpyraline ("histryl"); while chlorcyclizine ("histantin," "diparalene"), meclozine ("ancolan"), and buclizine ("vibazine") form a third group.

The substances which have been steadily added to the original antihistamines mepyramine (anthisan) and diphenhydramine (benadryl) have not greatly extended the scope of therapy. They differ from the original drugs mainly in two ways—first, in their rates of absorption and excretion, and secondly in the relative strength of other properties besides antihistamine action which all compounds of this type possess. It is thus possible to choose a drug with a brief or prolonged action, a drug which is a sedative or one which is not, according to the needs of the patient. It is also often found empirically that a particular patient will respond better to one drug than to another, even though statistics show the first drug to be less potent or to produce a higher incidence of toxic side-effects than the second.

Antihistamine Action

The action of all these substances on allergic symptoms is very similar. They act by combining with the receptors with which histamine normally reacts to produce its characteristic effects, and so they prevent the symptoms which result from the release of histamine. They have no direct action with histamine itself; they do not prevent the release of histamine from cells in response to injury or foreign substances, and they have no direct physiological action of their own which can account for their antihistaminic properties.

There are two consequences of this mode of action which are of practical importance in the treatment of allergy. The

first is that the administration of antihistamine drugs is only one part of the treatment, and must often be accompanied by measures either to prevent the release of histamine or to counteract its effects after it has been released, or both. The cause of histamine release may sometimes be removed by discovering the antigen responsible and desensitizing the patient. The release of histamine may also be suppressed by giving cortisone (Medical Research Council, 1956; Halpern, 1957). Finally the vasodilatation and fall in blood pressure due to histamine may be overcome by administering adrenaline or ephedrine, which have powerful properties opposed to those of histamine.

The second consequence of the competitive blocking action of the antihistamine drugs is that their effectiveness is limited by their ability to reach the site of action of the released histamine. While they are effective in about 60–80% of patients with urticaria or hay-fever, they are very rarely effective in asthma, even though histamine release has clearly been shown to be at least partly responsible for the symptoms of asthma. Sir Henry Dale (1950) suggested that the antihistamine drugs would be expected to prevent the action of "exogenous" histamine, which is liberated in one site, such as the epidermis, and acts on a site some distance away, such as the blood vessels, but would not prevent the action of "endogenous" histamine, liberated close to the receptors on which it acts. Schild (1956) showed that in segments of bronchial chain taken from asthmatic subjects at operation, mepyramine in a minute dose would prevent the contraction due to added histamine, but that a dose 10,000 times greater was necessary to prevent the contraction which was caused in the sensitized tissue when the appropriate antigen (pollen) was added. Smaller doses caused a graded reduction of the anaphylactic contraction.

It is still not possible to say how far the symptoms of asthma are due to histamine acting on receptors which the antihistamine drugs are unable to reach, and how far they are due to factors other than histamine. Halpern (1957) points out that the dyspnoea in asthma may be variously caused by oedema, spasm, bronchial congestion, secretory disorders, and imbalance of the autonomic nervous system. He has found that the antihistamine drugs are sometimes effective in treating asthma due to large protein molecules—for example, from feathers or animal danders—where the predominant symptom is oedema. Recently it has been shown (Hawkins, 1955) that a number of antihistamine drugs have a direct bronchoconstrictor action. This may be another factor contributing to the ineffectiveness of these substances in the treatment of asthma.

Another action of histamine on which the antihistamine drugs have no effect at all is the stimulation of gastric secretion. It has been suggested that the receptors for histamine in the gastric glands are of a different kind from those in smooth muscle, but there is no direct evidence for this.

In most allergic diseases the antihistamine drugs are very valuable in reducing the severity of the symptoms. In acute anaphylactic shock they may be life-saving. In serum sickness, urticaria, and hay-fever they are effective in a high proportion of patients. Their effects are, however, not always predictable, and some patients may fail to respond, or respond to one drug but not another, for unexplained reasons. There is no evidence that one antihistamine drug is more specifically effective than another in any particular form of allergic disease or type of patient. These unpredictable effects are not surprising, since the factors controlling

the release of histamine are still very incompletely understood. Much of the recent research on the problem has made use of histamine-releasing substances. These when injected into a normal subject cause symptoms identical with those produced when histamine is injected. In allergic patients, however, these initial symptoms are followed by reactions which closely reproduce the spontaneous symptoms of the individual's disease.

Other Properties

Drugs which act by combining with a histamine receptor will also be likely to have some effect on other physiological receptors. All the antihistamine drugs possess some anti-acetylcholine properties. They act like hyoscyne in causing sedation and inhibiting the vomiting reflex, and they cause side-effects such as dryness of the mouth and constipation. They are also local anaesthetics. The potency of these secondary actions is not proportional to the potency of the antihistaminic action.

The most strongly sedative drugs are diphenhydramine and promethazine ("phenergan"). Sometimes this sedative action is useful, but it is better not to give these drugs to patients who work during the day, and they may be dangerous when taken by drivers or people working with machinery. Moderate sedation is produced by mepyramine, tripelemamine, and bromazine, and the other drugs, though usually free from sedative effects, may induce drowsiness in some individuals. The patients should be warned of this possibility.

Diphenhydramine and promethazine are also highly effective in preventing travel sickness. They are usually given for this purpose in the form of their chlorotheophyllinate salts ("dramamine" and "avomine"). Meclozine is also effective in preventing sickness. Other antihistamine drugs have weaker anti-emetic properties; this action is not related to the antihistaminic activity.

The local anaesthetic action of the drugs is a useful additional property when they are applied to the skin to relieve the itching of urticaria or insect bites. Sensitization reactions, however, are rather frequent, and antihistamine creams are best not used indiscriminately for skin diseases (*British Medical Journal*, 1954).

The antihistamine drugs do not cause addiction. A few cases of agranulocytosis have occurred, but these have been rare considering how frequently the drugs are prescribed. They are dangerous poisons if swallowed by children, producing ataxia and convulsions which may be followed by fatal respiratory depression. The treatment (Craig, 1955) depends chiefly on gastric lavage and artificial respiration.

Administration

All these drugs can be given orally, and this is the usual method of administration for the treatment of allergic symptoms. Since a continuous action is required, the drugs are usually given several times during the day. Some of the drugs have a more prolonged action, and adequate treatment is possible with a single daily dose. The non-sedative drugs chlorcyclizine and diphenylpyraline may be given once daily. Chlorpheniramine is made in double tablets, in which half the dose is in the outer shell and half in a coated inner core for delayed action; they are effective for 8-10 hours. Promethazine also has a long-lasting action. Because of its sedative properties it should be given at night, and on the following day it continues to exert antihistaminic activity after the sedative effect has worn off. Meclozine is also given at night. When avomine and ancolan are taken to prevent travel sickness they should be taken on the night before the journey; dramamine should be taken every four hours.

The administration of the correct dose for each patient, giving relief from symptoms with minimum side-effects, is an important factor in treatment. The dose of any drug required by different individuals varies considerably, and the

amount needed by the same patient may also vary at different times, depending on such factors as the weather (for hay-fever subjects) and emotional stress.

When a rapid action is required an antihistaminic drug may be injected, and those which are suitable for injection are supplied in injectable form. Triprolidine ("actidil") is reported to act more quickly than the other drugs when given orally. Several of the drugs are supplied as creams and ointments, but they should not be applied too freely to the skin. Antazoline ("antistin"), which is the weakest and also the least toxic, is supplied as the phosphate for application to the eye and the nasal mucous membrane.

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THE PHARMACEUTICAL INDUSTRY

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The astonishing expansion of the pharmaceutical industry during the last quarter of a century, and in particular its even more accelerated growth during the past ten years, has, not surprisingly, resulted in certain conflicts. That there should be an undercurrent of disagreement between the industry and dispensing pharmacists is quite understandable, for the latter can claim that the expansion of the industry has resulted in an inevitable loss of prestige (and demonstration of skill), which for so long has been vested in the dispensing chemist. What is not so clear, except when considered in retrospect, is that the pharmaceutical industry should have become involved in a series of clashes with the medical profession and the State. The various aspects of this problem are here reviewed so as to establish, if possible, a better basis for understanding between the various parties involved.

Background to the Problem

The application of a critical approach came to medicine much later than it did to the other sciences. In 1865 Claude Bernard defined the attitude of modern medicine, emphasizing the absolute necessity of an experimental approach. This concept, when associated with the discovery of new synthetic compounds such as chloroform, "salvarsan," and aspirin, gave rise to what we now call pharmacology, a discipline which is so essential to any real advance in treatment. As compounds were synthesized it became necessary to screen them, and these functions were carried on for many years in the academic atmosphere of the university or technical college. In time, however, the complexity as well as the speed with which new compounds were produced necessitated the employment of various industrial techniques, so that more money had to be invested in the equipment of plant to make the compounds.

This transfer of emphasis from the academic to the industrial sphere resulted in the rise of a new class of technologists and scientists working for industry with a definite commercial aim as well as for the advancement of learning. Thus it was from industry that the next great advance, the sulphonamides, originated.

While progress continued in organic chemistry, equally great strides were made in biology. Unfortunately, when the probable therapeutic scope of penicillin was appreciated in 1941 there came coincidentally the realization that we in