ANTI-HISTAMINE DRUGS

By R. S. BRUCE PEARSON, D.M., F.R.C.P.

King's College Hospital

Histamine was first isolated from ergot by Barger and Dale in 1910. It was soon observed that its parenteral administration in animals caused effects resembling those of anaphylaxis (Dale and Laidlaw, 1911). In 1927 Best and others showed that it occurred naturally in animal tissues. Dragstedt (1945) has summarized the evidence in favour of histamine acting as the effective agent in allergy as follows:—

1. That its effects in animals are similar to those of anaphylactic shock.
2. That it is present in increased amount in mammalian tissue in anaphylaxis.
3. That many allergic manifestations in man are similar to the effects of released histamine.
4. That antihistamine drugs control many of the symptoms of allergy.

Lewis (1927), Curry (1946) and Epsteine (1943) have shown that various allergic manifestations, including urticarial wheals and asthma can be reproduced in man by histamine introduced locally. It is, however, well known that other naturally occurring drugs, particularly acetylcholine, may also induce asthma in asthmatic subjects.

The symptoms produced by injection or inhalation of histamine are more effectively prevented or abolished in animals by antihistamine drugs than are those caused by anaphylaxis. In the same way strips of sensitized guinea pigs' intestine, or the isolated uterus of a sensitized guinea pig, will still contract when brought into contact with antigen even after they have been rendered insensitive to the repeated effects of histamine itself (Schild, 1936; 1949). These apparent inconsistencies in the action of antihistamine drugs may depend on whether the histamine is liberated in close proximity to the sensitive end organs or at a distance so that they must diffuse through the tissues or be carried by the blood stream to the end organs (Dale, 1948). It is also possible that qualitative differences exist between the effects of histamine and anaphylaxis or allergy.

Nature of Antihistamine Drugs

Antihistamine drugs can be arranged in three chemical groupings. I am indebted to Dr. M. J. H. Smith, M.Pharm., F.R.I.C., for this classification:—

1. Ethylline-diamine derivatives (Anthisan, Pyribenzamine).

2. Alkylamine derivatives (Benadryl, Antistine).

3. Phenindamine derivatives (Thephorin).

The following drugs are at present available in this country:—

Anthisan (May and Baker).*

Antistine (Ciba).

Histostab (Boots).

Benadryl (Parke Davis).

Histantin (Burroughs Wellcome).

Pyribenzamine (Ciba).

Phenergan (May and Baker).

Thephorin (Roche Products).

Numerous other antihistamines are marketed in America but there is no reason to suppose that any of them are at present more effective than those available here.

Mode of Action

Antihistamine drugs are thought to exert their effect by competing with histamine for the tissue receptors, thus preventing the normal pharmacological action of histamine (Gaddum, 1948; Bain, 1949).

Methods of Assessment

Antihistamine drugs are assessed in the first instance by their action on animals. The following methods are used:—

1. Prevention of histamine flare in guinea pigs.

2. Prevention of death from histamine administered intraperitoneally, intrabronchially or intravenously (guinea pigs).

3. Prevention of anaphylactic death (guinea pigs, rats).

4. Prevention of the action of histamine on intestinal strips (guinea pigs).

5. Prevention of the effect of antigens on sensitized intestinal strips (guinea pigs).

In man their ability to prevent skin reactions caused by intradermal histamine or atopic extracts has been compared, as has their effect in asthma produced artificially by the inhalation of histamine. Finally their value can be estimated in the control of naturally occurring symptoms of allergy.

* Identical with Neo Antergan (Merck).

Because of the suggestibility of allergic patients, however, and of the tendency to spontaneous improvement, great caution must be exercised in assessing the results of treatment.

Relative Values

There is no exact parallel between the relative values of these drugs in animal experiment and human allergy. It has been shown that they vary widely in potency when tested against lethal doses of histamine. A standard protective dose of anthisan will protect guinea pigs against 124 lethal doses of histamine, whereas pyribenzamine protects against 37, benadryl against 5 and antistine against 2 (Friedlaender, 1948). Phenergan (Halpern, 1947) is said to prevent the effect of 1,500 lethal doses of histamine compared with a comparable dose of anthisan which protects against 80 lethal doses. In their ability to diminish the effect of intradermal histamine in man the differences between them are less striking although the drugs are effective in roughly the same order. In this respect phenergan is about seven times more effective than anthisan (Bain, 1949; Bain, *et al.*, 1949).

In clinical allergy the relationship between the action of the various antihistamine drugs is still less definite; thus one patient may receive no benefit from an antihistaminic powerful as judged by animal experiment, but may obtain relief from one far weaker. There is also a great difference in the duration of the effect of these drugs. Bain has compared the action of anthisan, phenergan and antistine in reducing the size of histamine wheals in the human skin. The maximum effect of all these drugs is reached 2 to 3 hours after ingestion by mouth; half the maximal effect is still present after 19 hours in the case of phenergan, 5 hours for anthisan and 3½ hours for antistine (Bain, 1949).

Side Actions

Antihistamine drugs also exert other pharmacological effects besides that of antagonizing histamine. All possess a strong local anaesthetic action. In most cases they are more potent in this respect than procaine; thus anthisan is 3.3 times as effective in its local anaesthetic action (Graham, 1947). Many also have an anti-acetylcholine effect which is not related to their antihistamine activity. Phenergan, for example, is strongly antihistaminic and also has a potent anti-acetylcholine action; anthisan, which is also strongly antihistaminic has only a slight anti-acetylcholine effect, while benadryl, which has a weaker antihistamine action, is a more potent antagonist of acetylcholine (Schild, 1949).

Benadryl, anthisan and pyribenzamine potentiate adrenaline in biological preparations; Thephorin, on the contrary, has an anti-adrenaline action. A hyoscine-like effect which causes drowsiness is commonly encountered, as is the atropine-like effect which causes dilatation of the pupils and a dry mouth. Anthisan has been shown to act like quinidine on the rabbit's heart (Dews and Graham, 1946). It is therefore evident that not all the effects of the antihistamine drugs can be attributed to their antihistamine activity.

These side actions may be advantageous in treatment—thus the potentiation of adrenaline and the anti-acetylcholine effect should increase the efficiency of drugs possessing these properties in allergy; the local anaesthetic action is undoubtedly partly responsible for their anti-pruritic effect, and sedation may be a useful addition to the antihistamine action at bedtime. In a few patients, however, the side effects are more pronounced than the antihistamine action, and may prevent their continued use. These side effects may be summarized as follows:—

SIDE EFFECTS		
Affecting Central Nervous System	Affecting Alimentary Canal	Miscellaneous
Drowsiness Fatigue Vertigo Fainting Narcolepsy Epilepsy Inco-ordination Loss of memory Paraesthesiae Insomnia Excitement	Nausea Vomiting Diarrhoea Colic Anorexia Dry mouth Constipation	Blurred vision Palpitation Muscular cramp Allergic reactions including asthma

Drowsiness is undoubtedly the commonest of these symptoms and is often accompanied by giddiness and fatigue. The highest incidence seems to occur after benadryl and phenergan, the lowest after antistine; diarrhoea and less often nausea and vomiting are seen more commonly after antistine than is drowsiness (Waldbott and Young, 1948). Pyribenzamine also causes a relatively high proportion of alimentary tract symptoms (Loveless and Brown, 1947; McGavack, *et al.*, 1948). It is interesting to note that success is claimed in the treatment of various forms of vomiting by antihistamine drugs. Thephorin differs from the other members of the group in that restlessness, excitement and insomnia sometimes occur and constipation is commoner than diarrhoea. Intensification of allergic symptoms including asthma following the use of anti-

histamine drugs has been described (Waldbott and Young, 1948).

There are considerable variations in the incidence of side effects according to different observers. Thus after benadryl, Loveless and Brown (1947) found that 60 per cent. of patients complained of drowsiness, whereas only 27.5 per cent. were affected in a series investigated by McGavack (1949). The incidence of side effects is related to the dose employed and there is considerable personal variation in sensitivity to different drugs. Patients showing side effects with one may tolerate another satisfactorily.

Side effects tend to diminish with continued use of the drug and they are only seldom severe enough to prevent further treatment. Drowsiness may be counteracted by amphetamine sulphate, nausea by taking the drug with food rather than on an empty stomach. Histamine phosphate has been suggested as an antidote if side effects are severe, but as these are probably seldom directly related to the antihistamine action, it is doubtful if this measure would be beneficial. Since histamine itself may cause severe symptoms in allergic individuals its administration might also be harmful. Because of the possibility of severe side effects antihistamine drugs should not be taken for the first time shortly before driving a motor vehicle.

Clinical Value

The antihistamine drugs which were first used in the atopic diseases have now been employed, with varying success, in a number of apparently unrelated conditions. Their value in the atopic diseases (asthma, rhinorrhoea, urticaria, angio-neurotic oedema) will first be discussed.

Atopic Diseases

There is unanimous opinion that these drugs are most effective in urticaria and angio-neurotic oedema. Successful treatment in from 70 per cent. to 100 per cent. of cases of this type have been claimed by various workers (Serafini, 1948; Gay, *et al.*, 1948; McGavack, *et al.*, 1948; Friedlaender, 1949; Bain, *et al.*, 1949; Levin, 1949). Some of these series are, however, very small and in many there is no differentiation between acute and chronic urticaria; it is well known that acute urticaria undergoes spontaneous recovery very readily and too much attention should therefore not be paid to figures relating to this condition. Chronic urticaria is, on the contrary, often highly resistant to treatment and symptomatic relief in adequately supervised cases is therefore very significant. Bain (1949) claims complete or considerable relief in 20 cases treated with phenegan prescribed in a single dose of 25 to 100 mgm. at night and almost equally good

results with anthisan given in doses of 100 mgm. three or four times daily. Good results are also claimed in rhinorrhoea and hay fever in from 52 per cent. to 89 per cent. (Loveless and Brown, 1947; McGavack, *et al.*, 1948; Waldbott and Young, 1948; Steinberg and Gottesman, 1948; Brown, *et al.*, 1948; Friedlaender, 1949; Poulsen, 1949; Knox, 1949). Gay and his co-workers (1948) claim success in these conditions in 68 per cent. of 428 cases treated with eight different antihistamine substances. Different workers adopt different criteria of success, the majority claiming 'partial success.' Those who subdivide their cases into 'complete' and 'partial relief' seldom claim more than 20 per cent. of completely successful results.

Asthma undoubtedly responds less satisfactorily, probably because factors other than allergy play a relatively more important part in its causation. Some confusion arises from the fact that asthma induced artificially by inhalation of histamine aerosol can be completely prevented or controlled by antihistamine drugs (Curry, 1946; Herxheimer, 1949). Unfortunately, naturally occurring asthma is much less susceptible. Partial relief is claimed in from 4 per cent. to 85 per cent. by various authors (Friedlaender, 1948; McGavack, *et al.*, 1948; Serafini, 1948; Gay, *et al.*, 1948; Waldbott and Young, 1948; Steinberg and Gottesman, 1948; Herxheimer, 1948; Friedlaender, 1949). Gay and his co-workers (1948), using dummy tablets as a control, claim over 50 per cent. relief in approximately 40 per cent. of 96 patients who were treated with antihistamine preparations. Hunter and Dunlop (1948), on the other hand, found that when the effects of anthisan and dummy tablets were compared in 35 asthmatic patients over a period of three months, no lasting benefit could be shown. They conclude that there is no indication for the use of antihistamine drugs in asthma and point out that the 'spontaneous fluctuations which occur in the severity and frequency of the attacks and the suggestibility of its sufferers to any form of treatment, especially if it is new and administered with impressive gravity, has made asthma the happy hunting ground for the uncritical therapeutic enthusiast.' Even those who believe that these drugs may be of value in asthma expressly state that they are ineffective in severe attacks (Loveless and Brown, 1947; Herxheimer, 1949), or if bronchial infection is present (Levin, 1946). The best results of treatment have been observed in mild cases of asthma which are disturbed by nocturnal wheezing. Phenegan or anthisan whose effects persist for a number of hours are then of value if taken before retiring at night. Under these circumstances the sedative side effects contribute to their therapeutic success.

Dermatoses

Various itching dermatoses including eczema are said to be relieved by the local or general administration of antihistamine drugs. There seems no doubt that these prevent the symptom of pruritus, and with the cessation of trauma due to scratching, improvement may then take place. It is possible that the anti-pruritic effect depends on their procaine-like rather than the antihistamine action.

Allergic Reactions to Atopic Extracts, Therapeutic Agents of Biological Origin and Drugs

In the course of desensitization with extracts of atopic materials (pollen, horse dander, etc.) general reactions, sometimes of a serious nature, occur from time to time. There is evidence that the antihistamine drugs are of value in preventing or controlling reactions of this type (Serafini, 1948). It is important to realize, however, that if the reaction is severe adrenalin is still the most effective and the most quickly acting remedial agent. Allergic reactions to biological preparations such as liver extract or insulin may be effectively controlled (Arbesman, *et al.*, 1946; Hunter and Hill, 1947; Leavitt and Gastineau, 1947; Klein, 1948; Caryer and Koelsche, 1948). The successful treatment of urticaria or anaphylactoid oedema as the result of sensitivity to drugs such as aspirin or penicillin has been recorded, as have similar symptoms in serum sickness (Cowan, 1949). It is also claimed that the respiratory symptoms of iodine (Boucher and Lafuma, 1948) and the nausea and vomiting caused by streptomycin (Bignell and Crofton, 1949) have been controlled.

Parkinsonism

A number of claims concerning the value of Benadryl in Parkinsonism have been made. The muscular rigidity and cramps are said to be chiefly affected, and bedridden patients are stated to have become ambulant (Gerest, *et al.*, 1948; Gates, 1949; Ryan and Wood, 1949). The effect of treatment is said to reach a maximum after ten days. Solonaceous drugs may be given at the same time. It seems possible that any benefit observed in this condition depends upon the atropin-hyoscine-like side effects of benadryl.

Nephritis

An allergic pathogenesis to bacterial products has long been postulated in acute nephritis. On this account antihistamine drugs have been used in its treatment. Craig, Clarke and Chalmers (1949) treated eight children suffering from this condition with anthisan and compared the time taken for the albuminuria to cease with a group of nine who had not received this treatment. The

average duration of albuminuria was 13 days for the treated cases and 92 days for the controls.

Radiation Sickness

It has been suggested that the symptoms of radiation sickness may be due to the liberation of histamine. Mains (1949) claims that the oral and local administration of benadryl and pyribenzamine (25 mgm. daily) in 300 patients have reduced the tendency to erythema and desquamation which often follows heavy dosage with X-rays. Lofstrom and Nurnberger (1946), also using benadryl, had previously claimed success in relieving the symptoms caused by X-ray treatment. Hunter and Dunlop (1948), using anthisan in alternate patients receiving X-ray treatment for carcinoma of the breast, were unable to demonstrate any benefit from its use.

Motion Sickness

Gay and Carliner (1949) have shown in a very well-controlled experiment conducted on troops crossing the Atlantic that dramamine (a compound of benadryl with theophylline), in doses of 100 mgm. every five hours, prevented sea sickness in almost 100 per cent. of cases. McEvedy (1949), comparing the effect of hyoscine (gr. 1/100) with anthisan (100 mgm.), also in a troopship, found that the latter was slightly more effective. Strickland and Hahn (1949) found that dramamine had some effect in preventing air sickness.

Vomiting of Pregnancy

Various workers have suggested that the toxæmia of pregnancy is the result of an allergic process, and that liberation of histamine might ultimately be responsible (Hofbauer, 1926; Kapeller and Adler, 1941 and 1943). Dougray (1949) claims that phenergan 25 mgm. t.d.s. is nearly always effective in controlling the vomiting of pregnancy; some cases however required heavier dosage. Anthisan also produced good results. Success has been claimed in pregnancy vomiting and other forms of pregnancy toxæmia with phenergan and antistine.

Prevention of the Common Cold

It is claimed that antihistamine drugs given within a short time of the onset of a cold are capable of aborting it (Gordon, 1948; Brewster, 1949). Colds commonly abort spontaneously in the early stages, however, and more controlled tests are necessary before these views are accepted.

Prevention of Side Effects caused by Curare

The use of curare-like compounds in anaesthesia and particularly in electrical convulsion therapy is not infrequently associated with bronchospasm,

excessive bronchial secretion and a well-marked fall in blood pressure. Various antihistamine drugs, including antistine, anthisan and phenergan, are said to be effective in preventing the side effects of curare and its analogues. These preparations were more effective than atropine (Courvoisier and Ducrot, 1948; Poulsen, 1949).

Time is necessary to show whether the antihistamine drugs will achieve a permanent place in the treatment of the conditions to which reference has been made. Many of these diseases are, like asthma, subject to natural fluctuations and the effects of suggestion; too often control cases have not been adequately studied. Even when antihistamine drugs are of proven value one must not be too ready to believe that this is due entirely to their antihistamine properties since they all have such important side effects.

Administration and Dosage

Oral. Antihistamine drugs are most often taken orally in the form of tablets or capsules. For chronic or recurrent conditions 150 to 300 mgm. can be given in 24 hours; in single doses 50 to 100 mgm. are usual. Antistine (histostab), which is less potent and also has fewer side effects than many of the others, is often given in doses of 100 to 200 mgm. Phenergan, at present the most potent of these drugs, may be effective in 25 or 50 mgm. doses; because its action is long lasting, one administration in 24 hours may be sufficient. Considerably larger doses of many of these drugs, up to 1,200 mgm. per day have been given (Bain, *et al.*, 1948; Knox, 1949; Southwell, 1949), but it is unwise to exceed the doses mentioned until it is certain that the patient does not show intolerance. A syrup containing 10 mgm. per dr. is put up by

some manufacturers for children.

Intravenous. In asthma and acute allergic conditions some drugs of this group have been given intravenously (Lofstrom and Nurnberger, 1946; Rosenberg and Blumenthal, 1949; Zolov, 1949). Rosenberg and Blumenthal (1949) used a solution of benadryl containing 10 mgm. per cc., and diluted each cc. with 30 cc. of normal saline; 30 mgm. were given slowly in this way. Side effects include drowsiness, severe headache and rigors. There seems to be little advantage in this method of administration.

Local application. In the itching dermatoses, ointments or creams containing 2 per cent. to 5 per cent. of anthisan, benadryl or thephorin may be effective (Wooldridge and Joseph, 1948). Instillations of 0.5 per cent. to 2 per cent. solutions into the eye or the nose has been recommended in conjunctivitis or hay fever (Friedlaender, 1948; Brem and Zonis, 1949; Zellen, 1949). Inhalation of 2 per cent. to 5 per cent. solutions in the form of an aerosol has been used in asthma.

Rectal. Gay (1949) gave dramamine rectally with success in severe sea sickness.

It should be remembered that sudden withdrawal of antihistamine drugs after regular treatment may lead to intensification of symptoms ('rebound phenomena') and the dose should therefore be gradually reduced. The American Council on Pharmacy and Chemistry (1949) have recently issued a warning against indiscriminate uses of antihistamine substances. Side effects may be dangerous in car drivers or those handling machinery at work, and they suggest that the amounts being taken for 'persistent colds' may exceed what has been established as normally safe. They also wisely point out that it is not yet certain that these drugs are harmless if taken continually for long periods.

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THE LEGAL DUTY OF THE DOCTOR AS REGARDS SKILL AND CARE

By A BARRISTER

Let us suppose that A goes to B and asks B to give him medical advice and attention. B is not a doctor and tells him so, but A says that he has every confidence in B's common sense and that is enough for him. If B then proceeds to treat A and does his best but, owing to his lack of the necessary skill and knowledge, A suffers some injury from the treatment, A will not have any remedy at law against B. He committed himself to B at his own risk and (to quote a legal phrase) B did not warrant his skill. In short, the beginning of a doctor's liability to his patient lies in the fact that the doctor warrants his skill and holds himself out as having the necessary skill and knowledge reasonably required for the discharge of the duties of his profession.

What kind of a liability is this? Is it a liability in contract or in tort? It is not necessary for me to deal with this distinction at any length. If a motorist carelessly knocks down a pedestrian and injures him, he is liable in damages, although he has no contract with the pedestrian and so committed no breach of contract by his careless driving. He is liable in tort. On the other hand, if I order

(say) potatoes of a certain quality and the tradesman accepts the order and then sends potatoes of an inferior quality, I have an action against him for breach of contract and I could not sue him unless I had a contract with him. In many instances a patient, whose doctor has failed to use proper care and has thereby caused some detriment to him, can sue the doctor in contract as well as tort. In some instances he cannot sue in contract but only in tort, e.g. suppose the carelessness occurs in the treatment of a patient who is brought into a hospital in an unconscious condition and occurs whilst he is still unconscious, the idea of a contract between the patient and the doctor would hardly seem appropriate to the circumstances. But I shall not for present purposes trouble about this distinction in the cause of action, as lawyers call it. The damages recoverable would probably be the same, whether the patient sued in contract or in tort or in both. I shall speak of the doctor's duty and treat the word 'duty' as covering the whole of the doctor's responsibility in law, whatever be the legal conception from which it is derived, and I shall speak of a breach of that duty