An Evaluation of Histamine as a Therapeutic Agent in Some Allergic Disorders*

JOHNNY A. BLUE, M.D., *Oklahoma City, Okla.*

The use of histamine in the treatment of certain diseases of sensitization has fallen into disuse. A re-evaluation of its efficacy is offered by the author.

IN THIS ERA OF SCARCITY OF HOSPITAL BEDS and rapidly changing therapeutic measures, along with the introduction of more potent and, shall we say, dangerous drugs to our armamentarium, one naturally looks with favor and a sense of well being on a proven remedy that has less risk to the patient and doctor than some of the newer and more popular drugs, steroids and corticosteroids, in the management of some allergic conditions. Such a drug is histamine.

This paper will be devoted chiefly to the use of histamine as a therapeutic agent mainly in allergic conditions where the antigen antibody is not demonstrable. By this I wish to make it clear that, in my opinion and most of the leaders in the field of allergy, histamine is of no value in the treatment of hay fever, asthma, allergic rhinitis, allergic eczemas, and such conditions where antigens and antibodies *are* demonstrable.

Horton[1] has said that histamine will prove to be one of the most valuable drugs the allergist has at his command. This is not universally accepted. There is a feeling by some that histamine is a drug of considerable interest but of little therapeutic importance.

The steroids and corticosteroids have overshadowed many of the older therapeutic measures. While attending medical meetings and visiting with men in the field of allergy and reviewing the literature, one notes the paucity of histamine being used intravenously or by iontophoresis in allergic conditions where antigen-antibody reaction is not demonstrable, as in allergic migraine[2] headache, post-traumatic headache, Meneire's disease, urticaria, serum sickness, et cetera.

The literature[3] on histamine is voluminous. Most of it deals with arguments on its therapeutic value and its relation to allergy and anaphylaxis.[4] Much is said about subcutaneous injections for desensitization. There are a few reports on its intravenous[2] use and by iontophoresis.[5] However, these deal mostly with investigative and hospitalized patients.

Because of the inability to get beds in the hospital for patients having severe acute urticaria or serum sickness, and because of the expense and the lack of desire of some patients who were less ill, to be hospitalized; it was decided to give histamine to these ambulatory patients in the office.

Most of these patients were referred cases who had received the usual therapeutic measures, such as diet, calcium, sedatives, glucose, ephedrine, antihistamine,[3] ACTH, and cortisone.

Intravenous Administration

Two methods of administration were used in this series of cases, the intravenous, and iontophoretic. Because the procedure was for the ambulant patient it was decided to give one intravenous infusion daily of the 2.75 mg. histamine acid phosphate in 250 cc. of normal saline. No attempt was made to count the drops. The infusion was given rapidly enough to produce a lasting flush during the intravenous procedure. The time used averaged about one-half to one and one-half hours. Some could tolerate it rapidly and some had to receive it very slowly. As high as four ampules (2.75 mg. each) were added to one infusion in some patients to

*Read before the Section on Allergy, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

obtain the therapeutic results. No patient was found who could not tolerate 2.75 mg. if given slowly enough.

The patients in most instances sat in a chair and read while receiving the infusion. There were two or three who were permitted to hold the intravenous bottles and walk to the window and watch the traffic or a parade with the needle in the vein, on special occasions.

All were instructed to take some food just previous to the injection. If "heartburn" developed, an anti-acid was given during the infusion.

On the average, two daily infusions were advised. In the pencillin urticaria and severe serum sickness type of reactions, most patients were asymptomatic after four to six injections. Some received fifteen or more infusions.

The age ranged from 5 to 70 years. Children seem to tolerate the drug as well as adults.

After the patient was asymptomatic and the intravenous therapy was discontinued, bi- or triweekly subcutaneous injections of histamine 1:1000 solution in large enough dosages to produce a mild flush was advised as a maintenance dose for a week or so in some of the severe cases.

Histamine by Iontophoresis

A direct current apparatus was constructed using a Burger's radio dry cell 45 volt battery for current. A milliamperemeter, with a reading of 0 to 25 ma., and a rheostat to keep from giving a shock, were connected to the apparatus. An electrode was prepared by folding Reynold's aluminum Wrap 3 inches wide and 8 inches long. To this was attached the positive pole of the B-battery.

Three sheets of Kleenex are folded three times, and 3 to 5 cc. of a 1:100 aqueous solution of histamine dihydrochloride (Imido Powder)* is applied evenly to the Kleenex. This in turn is applied to the patient's forearm with the aluminum electrode held firmly over it by elastic bandage or gauze, being careful that the pressure is generalized and that no metal is touching the skin.

The negative pole was similarly constructed except that a thin rubber sponge is used under the electrode and is dampened with normal saline solution to permit the current good conduction. This is attached in a similar manner to the opposite arm. The current is then turned on and gradually increased to 8 to 25 ma. according to the patient's tolerance. In several minutes a generalized flush is produced. The current is left on 15 minutes. The flush remains several hours and has a tendency to recur several hours later. It may be assumed that by this method the patient receives approximately 0.065 mg. of histamine per milliampere per minute through the skin.

This is repeated twice daily for a period of 10 days on the average. If further treatment is necessary, the patient may be instructed to administer further treatment with the apparatus at home where he can continue the schedule at his convenience.

*Supplied by Hoffman LaRoche (Imido Powder).

Discussion

Histamine rarely proves toxic in man. Excessive dosages will produce flushing followed by pallor, chilly sensation, metallic taste, pounding frontal headaches, rapid pulse and faintness, fall in blood pressure, visual disturbances, bronchial constriction, dyspnea, vomiting, coughing up of mucus, diarrhea, and in some cases, shock. Epinephrine will counteract these symptoms, however. In case of shock the normal blood volume should be restored.

There is increased flow of blood in the coronaries when histamine is administered, (we gave it to one patient who had had a coronary occlusion with no ill effect).

The site of action of histamine in the skin is the blood vessels where it causes dilatation and increased permeability.[6]

Histamine is potentially a strong activator of bronchiolar musculature. Its action is independent of and unaltered by atropine. It is believed to have little effect on the bronchi of normal persons, but is said to have very marked effect on persons with bronchitis, bronchial asthma, emphysema, and cardiac asthma. The violent dyspnea observed by some when histamine is administered intravenously is said to be due only partially to obstruction by muscle spasm of the bronchioles. Congestion and edema of the mucosa play a prominent part. (No such violent reactions were noted in patients in this series of cases studied.)

It has been the consensus of investigators that histamine would precipitate attacks of asthma when administered to asthmatics. Prince and Etter[7] found that this did not hold true in their cases. In our series of patients with a past history of asthma, only two showed any increase in their asthma and this was only an aggravation.[8] In only one of the latter were the asthmatic symptoms of any consequence. This would seem to indicate that the administration of histamine injections is no determining factor in deciding if an individual has an allergic state.[8]

There are only one or two patients with a previous history of duodenal or peptic ulcer in this series; none had an immediate flare-up of the ulcer, one had a recurrence of the ulcer several weeks after the treatment was terminated. This latter phase of histamine therapy has been the cause of conflicting views.[2]

Horton[9] found that histamine desensitization for histamine cephalgia in patients with an ulcer produced an improvement. McHardy and Browne,[9] using this as a criterion, attempted to treat active ulcer cases with histamine desensitization, but found that it caused such marked aggravation of symptoms that the treatment was abandoned.

Horton[10] observed that many of the beneficial effects of ACTH and cortisone in clinical use have been paralled by histamine therapy. It is his belief that histamine therapy causes release of these hormonal agents. If this be the case, it would be logical to assume that histamine therapy would be the safer and more conservative drug of choice in the treatment of conditions where it has proven of value rather than resorting to the corticosteroids.

"Most workers, however, seem to agree that there are no major inconsistencies to the assumption that the fundamental allergic reaction is identical with that of the anaphylactic reaction, and that histamine,[4] as one of the by-products of this reaction, is casually related to most of the phenomena."[9]

"The majority of workers seem to agree now, that the source of the histamine is in the tissues of the sensitized animal and that it is released into the blood and lymph as a consequence of the antigen-antibody reaction initiated by the re-injected antigen."[9]

"Many of the factors and idiosyncracies of anaphylactic syndrome remain unexplained—it also appears clear that the cellular discharge of histamine does not account for all the phenomena of anaphylaxis. . . . Nevertheless the question of the involvement of the chemical is progressing from suspicion and circumstantial evidence to more direct and convincing proof that it plays the fundamental role in the anaphylactic reaction."[9]

Histamine itself is not antigenic and does not induce antibody formation and thus does not act as a means of specific desensitization. Most workers seem to agree that repeated exposures of animal and man to the amine diminishes the susceptibility of a tissue to this substance. Ramévez and St. George[11] in 1924 were the first to attempt desensitization to histamine by repeated, increased doses. Karady, Smith and Katzenstein also verified this. Horton[1] developed his method of treating histamine cephalgia cases. After repeated and increased doses of histamine, he found that on repeated attempts to induce this type of headache by the injection of histamine the patients had developed a tolerance, and each attempt

TABLE 1

AN EVALUATION OF HISTAMINE AS A THERAPEUTIC AGENT IN SOME ALLERGIC DISEASES (191 CASES)

Method of Administration	*Acute Urticaria Serum-Sickness*	*Chronic Urticaria*	*Migraine*	*Histamine Cephalgia*	*Vertigo*	*Traumatic Headache*	*Multiple Sclerosis*	*Psoriasis*
(INTRAVENOUS 165)								
Results:								
Cured	68	23		3	2	1	1	
Improved	18	20	17	3			1	
Poor								
Failure	2	4	2					
(IONTOPHORESIS 29)								
Results:								
Cured	7	5		1				
Improved	2	7		2		1		1
Poor	1							
Failure		1						

required larger doses to precipitate an attack.

"The mechanism by which the favorable effects of histamine therapy is produced is not well known,"[12] however, it is generally conceded that its action is that of increased tolerance of the tissue to the substance released during the allergic reaction.

Prince and Etter[7] are of the opinion that histamine by its dilating effect on all of the capillaries around a hive brings about an absorption of the edema fluid and facilitates ridding the body of it by diuresis.

Histamine increases the output of epinephrine from the adrenal medulla.[4]

The above information and data were the principal stimulating factors in the treatment and presentation of this series of cases (Table 1).

Summary and Conclusion

A series of 194 cases treated with histamine by the intravenous and iontophoretic methods is presented.

It is concluded that this type of histamine therapy is very beneficial in acute urticaria, acute serum sickness-like disease, chronic urticaria, allergic headaches, migraine, vertigo, traumatic headaches, multiple sclerosis and psoriasis diseases.

Iontophoresis seems to be the therapy of choice due to its simplicity of administration, the less time involved in the administration, and the more persistent flush following its use, because of the production of deposits of histamine in the pores of the skin by this electrical technic.[13]

Histamine is a safe, harmless, therapeutic agent and is practically a specific for the serum sickness type of allergic reactions.

Bibliography

1. Horton, B.T.: The Use of Histamine in the Treatment of Certain Specific Types of Headaches, J.A.M.A. 116:377, 1941.
2. Thomas, William A., and Butler, Stuyvesant: Intravenous Histamine In the Treatment of Migraine, J.A.M.A. 128: 173, 1945.
3. Thomas, William A., and Butler, Stuyvesant: Intravenous Histamine and the Prescription of Migraine, Bull. New York Acad. Med. 22:425, 1946.
4. Dragstedt, Carl A.: Pharmacology and Role in Anaphylaxis, J. Allergy 26:287, 1955.
5. Abramson, Harold A., and Engel, Margaret: The Effects of Allergic and Histamine Wheals on the Rate of Absorption of Dyes and Blood From the Human Cutis, J. Invest. Dermat. 1:65, 1938.
6. Williams, Donald H.: Skin Temperature Reaction to Histamine in Atopic Dermatitis (Disseminated Neuro-Dermatitis), J. Invest. Dermat. 1:119, 1938.
7. Prince, Homer E., and Etter, Richard L.: Further Experiences with Histamine in Foreign Protein Type Reaction, Ann. Allergy 8:740, 1950.
8. The Letters Internat. Correspondence Soc. Allergists, Series 18:87, (Sept.), 1955.
9. Selle, W. A.: Histamine—Its Physiological, Pharmacological and Clinical Significance, Texas Rep. Biol. & Med. 4:138, 172, 1946.
10. Prince, Homer E., and Etter, Richard L.: Progress in Allergy, Ann. Allergy 10:215, 1952.
11. Selle, W. A.: Histamine—Its Physiological, Pharmacological and Clinical Significance, (1889), (Ramevez and St. George) Texas Rep. Biol. & Med. 4:138, 1946.
12. Tuft, Louis: Clinical Allergy, Philadelphia, Lea & Febiger, 1949, p. 525.
13. Abramson, Harold A.: Reactions to Histamine Iontophoresis in the Therapy of Multiple Sclerosis, Ann. Allergy 6:511, 1948.

Discussion (Abstract)

Dr. Boen Swinney, San Antonio, Tex. Dr. Blue is to be congratulated for again bringing to our attention the proper use of histamine in the treatment of some of the allergic and related diseases. I have heard a number of physicians remark that they have discontinued the use of histamine because of its failure as a therapeutic agent. Likewise, I have seen many patients come through my office on whom histamine has been used without the proper indication, and in some who have had the proper indication the histamine has been improperly administered. If we would but review Horton's original and some of his subsequent reports on the indications and use of histamine and follow his line, I believe we would all become enthusiastic in its use.

I have not adopted iontophoresis, perhaps I should, the reason being that in the instances of serum sickness and chronic urticarias in which I have used histamine have usually responded to just a few doses of 1:100 histamine intradermally. Usually 0.03 cc. is adequate to produce a moderate flush reaction and most have cleared up with just a few flushes. In most patients who have histaminic cephalalgia and who require treatment over a period of weeks and months, I try to get away from office procedures. In these, I teach the intelligent patients how to follow out Horton's schedule of treatment subcutaneously.

One point I would make in the use of histamine is this: there are several different preparations and dilutions on the market prepared by various pharmaceutical houses. As I had considerable difficulty with patients who take home treatment in securing the preparation I desire, I make up the dilutions in my own laboratory and supply the histamine to them, thus I know they are getting the proper dilution and proper preparation.

Dr. Henry Ogden, New Orleans, La. We cannot state that all cases of headache which appear after the injection of histamine fall into the category of Horton's syndrome (histamine cephalalgia). We must remember histamine is a vasodilator, and vascular headache is associated with increased amplitude of pulsation in the vessels, and that vasodilation may be present. I think if we follow Horton's description we must be cautious about including many of these cases as being true histamine cephalalgia. In my paper I pointed out that the injection of histamine will produce different types of vascular headache. This includes not only headache of the intracranial type (due to dilation of the intracranial vessels), but migraine, frontal headache, etc.

The injection of histamine may produce a generalized type of headache very quickly. This headache may last for only a few minutes. In histaminic

cephalalgia, a typical attack may occur within an hour after the administration of the drug. Therefore, just because histamine can be shown to cause headache we cannot necessarily say that the patient has histamine cephalalgia.

Dr. Harris Hosen, Port Arthur, Tex. I used histamine routinely some years ago for migraine. In the first few cases, the results were wonderful, the next few gave fair results, the next few, no results. I stopped using it. Some years later, I started again on this basis by giving 0.035 cc. of 2.75 mg. histamine subcutaneously, and if I could produce a headache that was almost identical with the headache from which the patient suffered, I would use it intravenously and I think I am getting somewhere with it. In that way I differentiate those cases in which I should not get results.

As regards time, I find in migraine it takes, as a rule, four or five hours to get in 250 cc. of saline with 2.75 mg. of histamine in it. If I let it run as much as 30 drops a minute, intense headache often is produced. I give 2 cc. of adrenalin (1:1,000,000) intravenously and it stops the reaction. I am just wondering whether it is necessary to give the whole amount. If one stops in an hour or two, one gives one-third of the dose and may get the same results.

I would like to know if the speaker has had similar experiences in the long time necessary to give the histamine in the patients having headaches.

Dr. Blue (Closing). I mentioned that it does not make any difference about how long it takes to give it, what you want is the flush. I have had some patients in whom it took two to three hours to get it, and maybe longer than this sometimes. I think the longer one gives the histamine, the better results one is going to get, and the more constant the histamine effect will be. Of course, it is rather hard to keep a patient in the office and tie one room up for four or five hours every day, or twice a day, as I did. All these patients were given the treatment in the office. I have had some who have had headaches with treatment; one can give too strong a solution, and those are the patients with whom one has to be cautious. Someone must watch these all the time. In intravenous therapy the turning of the arm or something like that will increase the drops and I think a lot of times the reason one gets poor results is because one does not have constant watching of the patient. If the needle is against the wall of the vessel, not as much will be delivered as if it is turned up. I have had some patients do this themselves, and thus regulate the dosage. They get rather accustomed to those things. I think the constant getting of the histamine, whether by deposit or intravenously, is the thing.
