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THE EFFECTS OF ANTIHISTAMINE SUBSTANCES ON THE RESPONSE TO HISTAMINE OF THE BLOOD VESSELS OF THE HUMAN FOREARM

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Antihistamine drugs have been used by various workers (Emmelin and Emmelin, 1947; Folkow, Haeger and Kahlson, 1948) to investigate the dilator mechanisms in the peripheral circulation of animals. Since such mechanisms in man may conveniently be examined in the limbs (Landowne and Thompson, 1948), we have investigated the effects of antihistamine drugs introduced into the arterial circulation of a limb and observed their local action on the forearm vessels, their effect on the response of the forearm circulation to various doses of histamine, and the duration of this effect.

METHODS

The forearm blood flow was measured by venous occlusion plethysmography (Barcroft and Swan, 1953) with temperature-controlled plethysmographs at 34–35° C. (Greenfield, 1954). Four records of flow were usually made in each min. and the average of these taken as the flow in that min. and expressed in ml. of blood/100 ml. of tissue/min.

Intra-arterial infusions were given through a needle connected by polythene tubing to a mechanically driven syringe and inserted centrifugally, through an anaesthetized area of skin, into the brachial artery at the elbow. Two syringes could be driven simultaneously and the infused solution thus changed without delay. An infusion of physiological saline was maintained at a rate of 4 ml./min. except when the drug solutions, made up in physiological saline so that the dose for 1 min. was contained in 4 ml., were being given. In some expts. infusions were given into an antecubital vein.

The antihistamines were: tripelennamine hydrochloride ("Pyribenzamine"), antazoline ("Antistin"), and mepyramine maleate ("Anthisan"). The amount infused into the brachial artery was usually half the intravenous dose recommended by the manufacturers and was usually given over a period of 5 min.

Histamine acid phosphate (1:1,000, B.D.H.) was given intra-arterially in doses of 1, 5, 10, or 20 μg./min. for periods of either 3 or 5 min. Doses are expressed as the weight of the salt.

The room temperature was 20–22° C. and the subjects (colleagues and medical students) were recumbent for at least half an hour before observations were begun.

RESULTS

General Effects of Antihistamines

In a total of 26 expts., in which 12.5 mg. of tripelennamine, 50–100 mg. of antazoline, or 25 mg. of mepyramine were given into the brachial artery, no general effects were experienced by the subjects either during or after the infusion.

Intravenous infusion of these doses of tripelennamine and antazoline usually had no general effects. In one subject, however, 25 mg. of tripelennamine intravenously caused, during the infusion, sensations of dizziness, slight nausea and tingling in the limbs. These symptoms passed off during the subsequent 45 min. Similar symptoms occurred in one subject after 25 mg. of mepyramine; the effects were more persistent than with tripelennamine and the drowsiness lasted for 5 hr.

Local Effects of Antihistamines

Tripelennamine (2.5 mg./min. for 5 min. in 9 expts.) infused intra-arterially caused a fall in blood flow during the infusion to about half the resting value, but antazoline (10 mg./min. for 5 min. in 9 expts.) and mepyramine (5 mg./min. for 5 min. in 3 expts.) caused a twofold increase in flow. After tripelennamine there was a further slight fall and the flow usually remained at this lower value throughout the remainder of the expt. (Fig. 1). After antazoline and mepyramine, however, the blood flow gradually fell to, or a little below, the previous resting level when the infusion ceased.

When the intra-arterial infusion of antazoline (5 expts.) or mepyramine (1 expt.) was repeated, up to 34 min. later, the dilator effect was not reduced.

No effect on forearm blood flow was detected during intravenous infusion of any of the antihista-

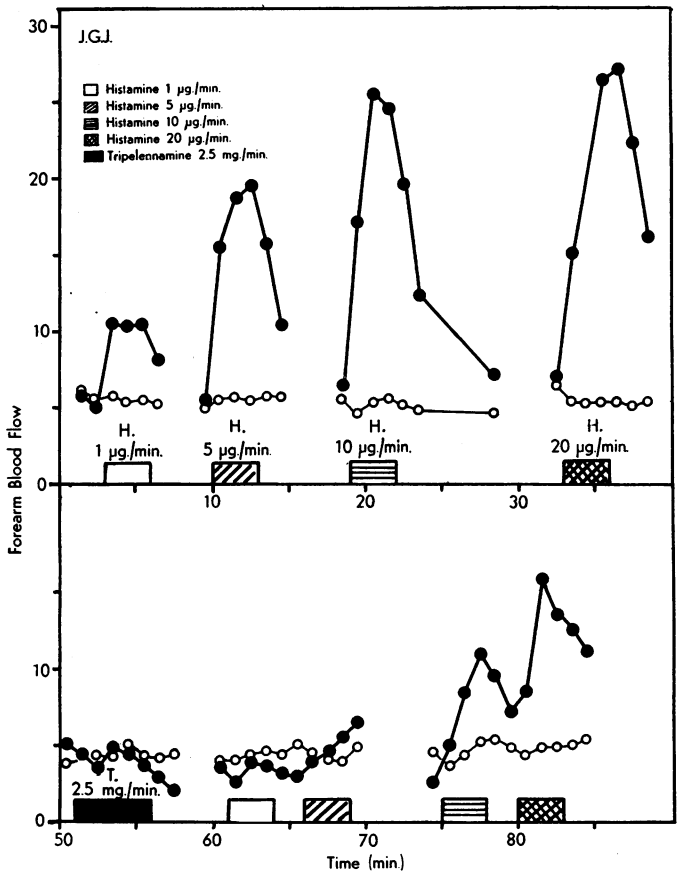

FIG. 1.—The response in one subject of the forearm circulation to four different doses of histamine infused into the brachial artery before and after infusion of tripelennamine. The forearm blood flow is expressed in ml./100 ml./min. and each symbol represents the average of four observations of flow taken in 1 min. The closed circles indicate the flow in the injected forearm and the open circles that in the opposite forearm.

mine substances (5 expts.). In one of these expts. both the hand and the forearm blood flows were measured while antazoline was given intravenously in successive doses of 1, 2, 5 and 10 mg./min. each for 5 min. There was no alteration in the flow.

In 1 expt. in which the skin was observed during the intra-arterial infusion of 50 mg. antazoline in 5 min. there was a slight flush of the forearm skin and there was a feeling of distension and tingling in the arm. A second infusion of the same dose 18 min. later had no such effects. This was the only occasion on which symptoms were noticed in the forearm with any of the antihistamines. Usually the effect of the antihistamines on the skin colour was not observed because of the plethysmograph on the forearm.

Effect of Intra-arterial Antihistamines on Histamine Response of Forearm Vessels

This was determined in the following way. The blood flow was measured throughout in both forearms. The vasodilator response of one forearm was first observed to doses of 1, 5, 10, and 20 μg./min. of histamine given in that order into one brachial artery. The flow on the injected side was allowed to return to the base-line value between the doses of histamine. The antihistamine substance was then introduced into the brachial artery, the flow being measured continuously. Histamine infusions were then repeated in the same doses and order as before. Finally, at the end of the expt. to determine whether the effectiveness of the antihistamine had diminished, a further dose of 1 μg./min. of histamine was given and the response compared with that immediately following the antihistamine.

Fig. 1 shows the results of a typical experiment with tripelennamine.

Tripelennamine, in a total dose of 12.5 mg., reduced the responses of the forearm circulation to all four doses of histamine (Fig. 2A) and was still effective at the end of the series. In A.H.G.L. the response to 1 μg./min. of histamine was abolished; the responses to 5 and 10 μg./min. were less than, and that to 20 μg./min. little more than, the response to 1 μg./min. before the antihistamine had been given. The effect in J.G.J. was similar. Some further results with tripelennamine are shown in Fig. 3A.

Mepyramine was less effective than tripelennamine as an antihistamine (Fig. 2), and there was some recovery from its antihistamine effect by the end of the expt.

Antazoline was almost as effective as mepyramine in reducing the dilator responses to 1 μg./min. of histamine, but the effect on the responses to the higher doses was less marked (Fig. 2C). This was probably due to the wearing off of the antihistamine effect by the time the higher doses were given, because at the end of the series (¾–1 hr. after the injection of antihistamine) the response to 1 μg./min. of histamine had almost recovered in P.J.G. and was greater than before

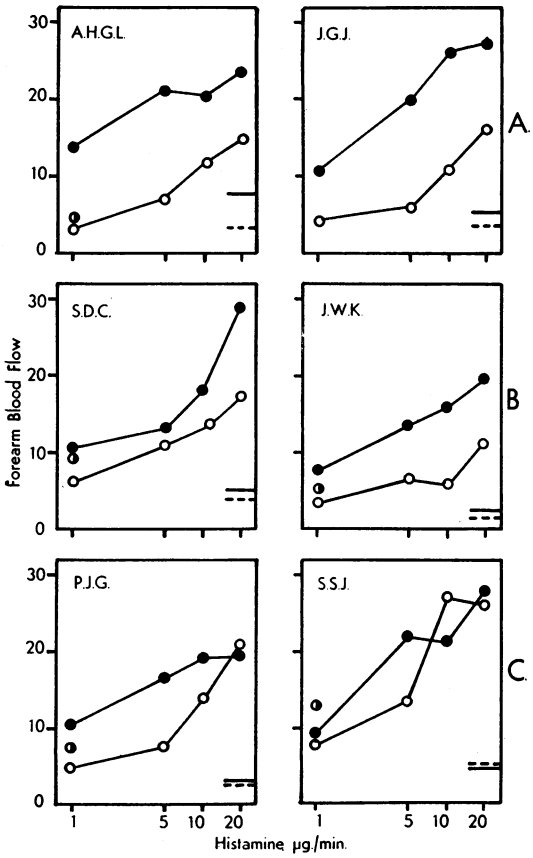

FIG. 2.—The response of the forearm circulation to histamine before and after intra-arterial infusion of A, tripelennamine (12·5 mg.), B, mepyramine (25 mg.), and C, antazoline (50 mg.). The forearm flow is expressed in ml./100 ml./min. and the abscissa represents the dose of histamine in µg./min. on a log. scale. The symbols represent the average of the highest four flows during the 3 min. periods of histamine infusion. ● before antihistamine; ○ 15 min. after antihistamine; ◑ 1–1½ hr. after antihistamine; —— resting level of flow before antihistamine; - - - - resting level of flow after antihistamine.

in S.S.J. The additional data shown in Fig. 3B confirm that antazoline is less effective than tripelennamine.

Effect of Repetition of Antihistamines.—In 5 expts. an attempt was made to increase the effectiveness of antazoline by giving a second dose after the first had been tested by histamine infusions. Fig. 4 shows the results on one of the subjects. The inhibiting effect of the first dose of antazoline was not very satisfactory, but a second dose did not further inhibit the effect of 5 µg./min. of histamine. The data for all 5 expts. with antazoline, and for 1 with mepyramine, are shown in Table I. The effectiveness of an antihistamine was never increased by a second dose.

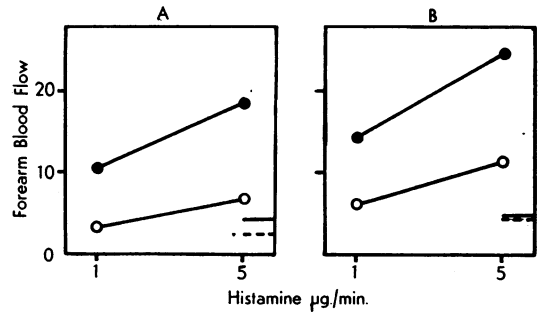

FIG. 3.—Averaged data from expts. in which A, tripelennamine (8 expts.), and B, antazoline (6 expts.), were used in investigating histamine release in the forearm. The symbols represent the highest four flows during infusion of histamine in doses of 1 and 5 µg./min. before (●) and after (○) antihistamine. The forearm flow is expressed in ml./100 ml./min.; —— resting level of flow before antihistamine; - - - - resting level of flow after antihistamine.

Effect of Intravenous Antihistamines on Histamine Response of Forearm Vessels

The effect of intravenous administration of tripelennamine (12.5 mg. in 5 min.) on the response of the forearm circulation to intra-arterial histamine was investigated in one subject (Fig. 5A). This dose of antihistamine given in this way is less effective and less persistent than is the same dose given intra-arterially (Fig. 2A). One hour after administration of the antihistamine the responses had returned to normal.

Effect of Intra-arterial Antihistamine on Histamine Response of the Opposite Forearm

The validity of the opposite forearm as a control in expts. in which antihistamine is given intra-arterially depends upon whether or not sufficient antihistamine enters the general circulation to affect the histamine response of the opposite forearm.

TABLE I

EFFECT OF REPEATED DOSES OF ANTIHISTAMINE ON THE FOREARM RESPONSE TO HISTAMINE

Subject and Rate of Histamine Infusion		Average of Highest 4 Flows During Histamine (ml./100 ml./min.)		
		Before	After 1st Dose	After 2nd Dose
		Antazoline		
A.D.M.G.	1 µg./min.	14·6	6·2 (50 mg.)	8·1 (50 mg.)
	5 µg./min.	25·8	14·7	14·7
S.P.D.	5 µg./min.	16·6	12·4 (100 mg.)	13·7 (100 mg.)
I.V.A.	1 µg./min.	12·2	6·1 (50 mg.)	6·2 (50 mg.)
J.J.	5 µg./min.	13·2	9·6 (20 mg.)	8·9 (20 mg.)
R.F.W.	4 µg./min.	22·0	12·1 (40 mg.)	11·3 (60 mg.)
	0·75 µg./min.	—	5·9	5·9
		Mepyramine		
J.R.	1 µg./min.	6·9	4·0 (25 mg.)	3·8 (25 mg.)
	5 µg./min.	10·2	5·8	6·1

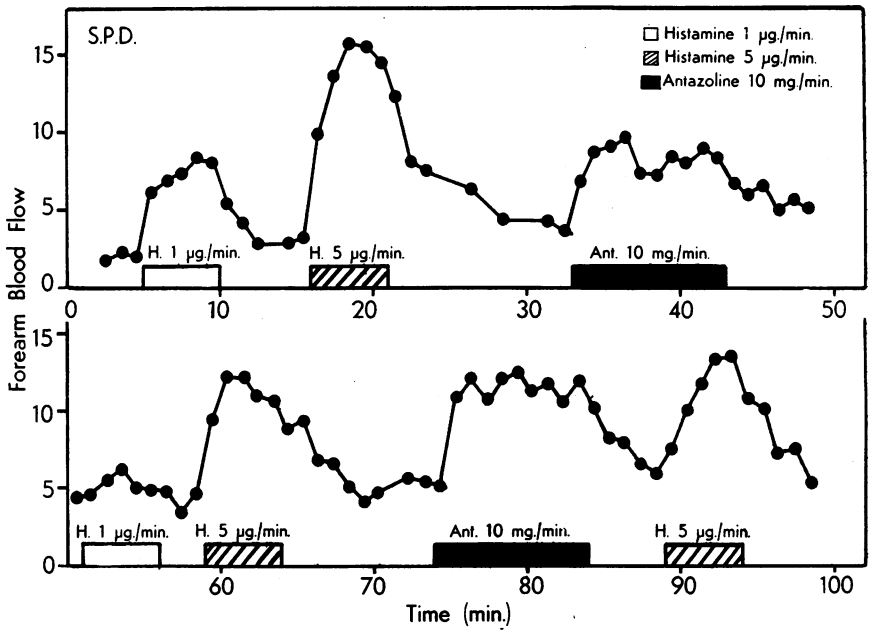

FIG. 4.—The response of the forearm circulation to 5 min. infusions of histamine before and after intra-arterial infusions of antazoline. The conventions are the same as in Fig. 1. Two doses of antazoline were given, each of 100 mg. over 10 min. The flow through the injected forearm only is shown.

Fig. 5B shows an expt. in which the effects of injecting histamine at 1 and 5 μg./min. into the left brachial artery were observed before and after injecting 12.5 mg. of tripelennamine in 5 min. into the contralateral brachial artery. The response to histamine was conspicuously reduced, but less so than after injection of tripelennamine into the ipsilateral brachial artery on another occasion. The responses to both 1 and 5 μg./min. of histamine, in terms of the maximum increase above the previous resting level, were reduced to about two-thirds of those before the antihistamine, whereas in all 9 expts. in which tripelennamine was infused intra-arterially, and the histamine responses measured in the forearm of the same side, the responses to 1 μg./min. were almost abolished and those to 5 μg./min. reduced to less than one third.

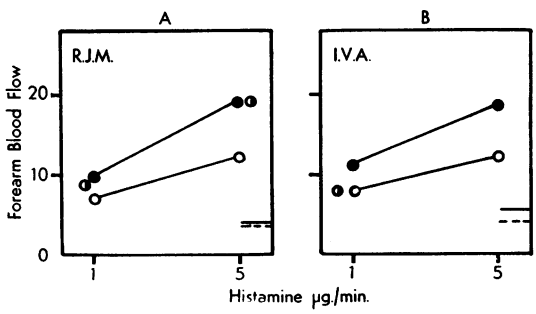

FIG. 5.—A, The response of the forearm circulation to intra-arterial histamine following intravenous infusion of 12·5 mg. of tripelennamine. B, The response of the circulation through the left forearm following infusion of 12.5 mg. of tripelennamine into the right brachial artery. The conventions are the same as in Fig. 2.

Intra-arterial Antihistamines on the Response to Electrophoresis of Histamine into Skin

In one subject histamine was administered by electrophoresis into the flexor surface of the forearm before and after the infusion of 50 mg. of mepyramine into the brachial artery. Before the antihistamine was given this procedure resulted in, first, a redness of the circular area in contact with the histamine solution, then an irregular flare, and, finally, a circular weal over the central area. Sixty min. after the mepyramine had been given, and shown to be effective in reducing the responses of the forearm blood flow to intra-arterial doses of 1 and 5 μg./min. of histamine, the procedure was repeated. The circular area of redness was obtained as before, but neither the flare nor the weal developed.

DISCUSSION

The antihistamine substances tripelennamine, antazoline and mepyramine when introduced intra-arterially into the forearm, in half the intravenous dose recommended by the makers, are effective in reducing or abolishing the dilator response of the forearm circulation to histamine introduced by the same route. Tripelennamine and

mepyramine were more satisfactory than antazoline and their effect persisted for at least 1–1½ hr. whereas antazoline had usually ceased to be effective at the end of this time. It was not possible in a single expt. to assay the effect of the antihistamine on the response of the forearm flow to various doses of histamine given in different sequences because of the length of time required for one sequence, largely taken up in waiting for the blood flow through the forearm to return to the resting value between histamine infusions. Recording the responses to 4 doses of histamine before and after an infusion of antihistamine occupied about 3 hr., and this was as long as even a trained subject was content to lie with both arms supinated and immobilized in plethysmographs and with a needle in one brachial artery. With tripelennamine the weaker effect on the responses to the larger doses of histamine was not due to the wearing off of the antihistamine effect, because when 1 μg./min. of histamine was repeated at the end of the series the response was still almost or completely abolished. With antazoline, however, the absence of any reduction of the responses to the higher doses was almost certainly due to the short duration of the effect of the drug as shown by the presence of a normal response to 1 μg./min. of histamine at the end of the series. With mepyramine the responses to the higher doses showed considerable reduction, but there was some recovery by the end of the expt.

Antazoline and mepyramine both had a sustained dilator effect on the forearm vessels while they were being infused into the brachial artery, and this effect recurred on repetition of the dose. Thus, although it has been shown that antihistamines may act as histamine releasers (Pellerat and Murat, 1946 ; Arunlakshana, 1953) it appears that the increase in flow produced by the antazoline and mepyramine is unlikely to result from the release of histamine at a site accessible to the antihistamine action of the drugs.

Repetition of the antihistamine did not increase its effectiveness in reducing the response to histamine. Whether the antihistamine effect might have been enhanced by further increasing the dose of the drug is not known, since, in order to avoid undesirable side effects, amounts of more than 200 mg. have not been given. Folkow *et al.* (1948) found in the cat that increasing the dose of diphenhydramine above a certain value did not increase the antihistamine effect.

Histamine in a dose of 1 μg./min. causes an increase in forearm flow to about 10 ml./100 ml./min. and 5 μg./min. increases it to about 20 ml./100 ml./min. The ability of the intra-arterial antihistamine substances to reduce or abolish these responses suggests that the antihistamines could be used in the investigation of dilator phenomena in the forearm. The intra-arterial administration has the advantages that it produces a high local concentration, and that the dose of antihistamine can be kept below that which induces unpleasant or undesirable side effects. The most effective reduction of histamine responses was achieved with tripelennamine, and its duration of effect of at least 1–1½ hr. would enable observations of most vasodilator phenomena to be made while the drug was still effective. The individual variation in degree and duration of effect of the antihistamines makes it desirable that in any such investigation a check be made on the effectiveness of the drug in inhibiting histamine responses before and after the observations on the vasodilator phenomenon.

The value of the antihistamine introduced intra-arterially in the investigation of the possible rôle of histamine in vasodilator phenomena of the forearm depends upon whether the antihistamine so introduced is as effective in counteracting the response to histamine released in the tissues as it is in counteracting that introduced into the artery. Since the triple response caused by electrophoresis of histamine into the skin is abolished by antihistamine introduced intra-arterially, it seems likely that the antihistamine would reach the site of action of released histamine on the vessels, but it is possible that the histamine released from the tissues is in a form not amenable to counteraction by antihistamine. Our expts. provide no evidence on this point.

The fact that the introduction of tripelennamine into the brachial artery of one side resulted in a reduction of the response to histamine of the opposite forearm circulation indicates that, although the antihistamine was not entering the general circulation in sufficient quantities to cause any symptoms, enough was arriving in the forearm to reduce its response to histamine. The extent of this reduction (Fig. 5B) was approximately as great as that produced by the same dose given intravenously (Fig. 5A). Although only 2 expts. of this sort have been carried out, and individual variations in the response of the forearm both to histamine and to antihistamine might account for this similarity, it suggests that a considerable proportion of the intra-arterially introduced antihistamine enters the general circulation and reaches the opposite forearm. This implies that, in the investigation of the possible rôle of histamine in the cause of a vasodilator phenomenon

of the forearm, the opposite forearm cannot be used as a control, since the response to any histamine present or released there will be modified in the same way as, though to a lesser extent than, on the experimental side.

Summary

1. The effectiveness of intra-arterial tripelennamine, mepyramine and antazoline in inhibiting the response of the forearm circulation to histamine has been investigated.

2. Half the recommended intravenous dose of each drug abolishes, or almost abolishes, the response to 1 μg./min. of histamine given intra-arterially and very considerably reduces the responses to higher doses.

3. The greatest and most prolonged effect was from tripelennamine and the least and shortest effect from antazoline.

4. Repeating the dose of mepyramine and antazoline did not increase the antihistamine effect.

5. The intra-arterial administration of antihistamines in the investigation of the rôle of histamine in vasodilator phenomena of the forearm is discussed.

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