

THE INFLUENCE OF AN ANTIHISTAMINE DRUG ON THE RELEASE OF HISTAMINE IN THE UNANAESTHETIZED DOG

BY

W. D. M. PATON AND M. SCHACHTER

From the National Institute for Medical Research, Mill Hill, London, N.W.7

(Received May 18, 1951)

There is evidence that the histamine content of the blood increases under a variety of conditions, including anaphylaxis, and after the administration of adrenaline, the wetting agent Tween 20, and a variety of organic bases (Feldberg, 1941; Krantz, Carr, Bird, and Cook, 1948; MacIntosh and Paton, 1949). Little information has been acquired, however, about the ability of the antihistamine compounds to influence the process of histamine release. Wells, Morris, and Dragstedt (1946), in only two experiments showed that, despite protection with benadryl, the anaphylactic reaction was accompanied by high levels of plasma histamine. This indicates that benadryl does not prevent the release of histamine in anaphylaxis. Staub (1946) claims, however, that the release of histamine into the blood after administration of adrenaline to man is prevented by antistin. Grossman and Robertson (1948), using the gastric secretion of the total stomach pouch of dogs as an index of released histamine, observed that the gastric secretion following administration of Tween 20 was greatly reduced by benadryl.

The interpretation of these results is difficult, particularly since neither antistin (Reuse, 1948) nor benadryl (Schild, 1947) is a specific antihistamine, and since the total pouch used by Grossman has unusual secretory characteristics (Woodward, Dragstedt, Tovee, Oberhelman, and Neal, 1945). So much importance, however, both theoretical and practical, attaches to any drug which can modify the process of histamine liberation that we have further examined the problem. As an index of histamine release we measured the hydrochloric acid secreted by the intact cannulated stomach of trained dogs. Mepyramine maleate (neoantergan) was selected as an antihistamine because of its high specificity (Schild, 1947; Reuse, 1948). The histamine liberator Compound 48/80, a condensation product of *p*-methoxyphenylethylmethylamine and formaldehyde (Baltzly, Buck, de Beer, and Webb, 1949; Paton, 1951), provided a simple means of obtaining a gradable histamine-releasing action without tissue destruction or signs other than those due to histamine release. In a few experiments, another histamine liberator, propamidine (MacIntosh and Paton, 1949) was used.

METHODS

Four dogs, weighing between 10 and 20 kg., trained to stand quietly in a frame for hours, were equipped with gastric cannulae made of monel metal. Under these conditions the gastric reaction was always alkaline unless we deliberately took measures

TABLE I

GASTRIC SECRETION IN RESPONSE TO COMPOUND 48/80 WITH AND WITHOUT MEPYRAMINE
Compound 48/80, 10 mg. subcutaneously in all experiments. *Italic figures refer to experiments in which 2 mg. mepyramine per kg. was given subcutaneously 15 min. before Compound 48/80*

Dog	c.c. 0.1N-HCl secreted on days:				Ratio of secretion after 48/80 + mepyramine to secretion after 48/80 alone
	1	3	10	12	
Spot	25	10	10	6	1.55
Dusky	60	<i>124</i>	<i>106</i>	14	3.11
Jackie	<i>103</i>	45	21	5	1.64
Blackie	32	37	40	19	1.52
Total	220	216	177	44	Av. 1.95

to stimulate secretion. The amount of saliva collected from the cannula over a period of 1-2 hours is not more than a few c.c., which did not interfere with the "total" hydrochloric acid titrations, since phenolphthalein was used as indicator. Regurgitation of bile is a rare occurrence under these conditions. Compound 48/80 was given as the chloride, propamidine as isethionate, mepyramine as maleate, and histamine as acid phosphate. All drugs were administered subcutaneously. The thickness of the jowl of the upper jaw about 1-2 in. from the snout was measured in duplicate with a micrometer modified so that the jowl was enclosed between two flat surfaces during measurement. A lightly loaded spring ratchet enabled the reading to be taken with a reproducible gentle pressure, so that the maximum error with repeated measurement was 0.5 mm. In the experiments of Table II, the tests on each pair of dogs were crossed over, as indicated.

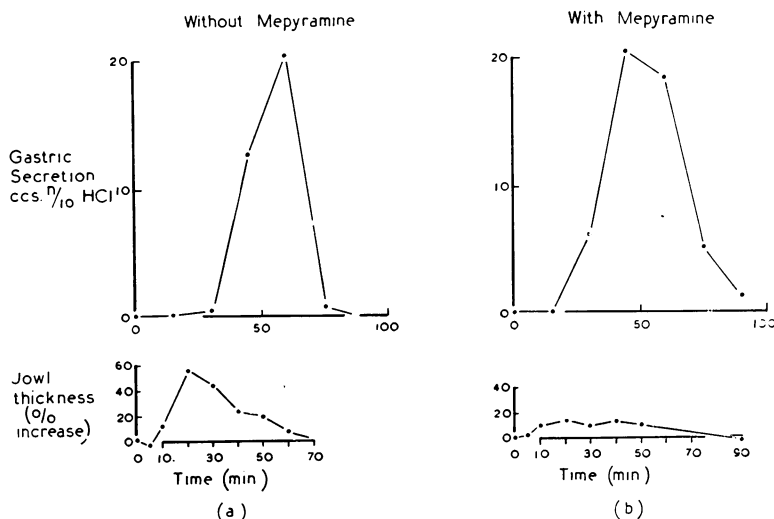


FIG. 1.—Dog Jackie. Gastric secretion (c.c. 0.1N-HCl per 15 min. sample: upper curves), and increase in jowl thickness (%: lower curves), in response (a) to 10 mg. Compound 48/80 subcutaneously at zero time, (b) to 10 mg. Compound 48/80 subcutaneously at zero time, with mepyramine 2 mg./kg. subcutaneously 15 min. previously. (a) and (b) are each the average of two crossed-over tests.

RESULTS

The subcutaneous injection of 10 mg. Compound 48/80 into a dog always produced signs of severe itchininess, facial swelling, and secretion of gastric juice lasting 1–2 hours (Fig. 1). The facial swelling was particularly marked in the bristle area near the mouth, the eyelids, and the pinna of the ear; these areas also showed considerable erythema. Oedema and erythema of other regions was not observed, except for the nipple area in one animal. The gastric secretion produced by this dose of Compound 48/80 corresponded to that elicited by 1–2 mg. histamine acid phosphate.

Although the facial swelling and the signs of pruritus were almost entirely abolished by mepyramine, the gastric secretion was never diminished and usually considerably increased (Fig. 1, Table I). Further evidence that this dose of mepyramine was effective against either injected histamine or the circulatory depressor action of a liberator was that in the anaesthetized animal the depressor action of the liberator was reduced, and that in an unanaesthetized animal weal formation by intradermal injections of histamine was antagonized. It follows that an otherwise effective dose of mepyramine did not reduce the amount of histamine released by Compound 48/80.

The question now arises why the gastric secretion should actually be increased by mepyramine. The possibility that under these circumstances mepyramine alters the response of the gastric glands to histamine was excluded by demonstrating that in the same four dogs the gastric secretory response to injected histamine was not significantly altered by the same dose of mepyramine (Table II). Another explanation, however, may be that associated with the swelling and oedema of the face there is an oedema of the gastric mucosa, which is known to reduce gastric

TABLE II

EFFECT OF MEPYRAMINE ON GASTRIC SECRETION PRODUCED BY HISTAMINE
Histamine, 1 mg. subcutaneously. Mepyramine, 2 mg./kg. subcutaneously given 15 min.
before histamine

Dog	c.c. 0.1N-HCl produced by		Ratio <i>b/a</i>
	Histamine <i>a</i>	Histamine + Mepyramine <i>b</i>	
Spot	22.1	25.0	1.13
Dusky	34.4	23.1	0.67
Jackie	84.6	65.1	0.77
Blackie	38.0	51.4	1.35
Total	179.1	164.6	Av. ratio = 1.02

secretion (Ricketts, Kirsner, and Palmer, 1949). The action of mepyramine in preventing this oedema would then allow the gastric secretion to proceed unimpeded during a period when it would otherwise be inhibited. Some support for this was obtained by the observation that the gastric mucosa was congested and oedematous to direct inspection in a dog anaesthetized after injection of Compound 48/80; also, in our unanaesthetized dogs, in the absence of mepyramine

the gastric secretion resulting from Compound 48/80 did not become maximal until the facial oedema began to decline.

Propamidine was tested in the same way, and it also produced gastric secretion, facial oedema (cf. Lourie and York, 1939), and itching; as with Compound 48/80, a vigorous gastric secretion was obtained in the presence of mepyramine. Similarly, gastric secretion in an anaesthetized animal following continuous infusion of propamidine was not significantly altered by mepyramine in the same dose. Propamidine, however, proved unsatisfactory for the purpose of this investigation, because after receiving several injections the animals gradually became moribund and had to be sacrificed. This drug was therefore used in only a few experiments.

Development of refractoriness to compound 48/80

With repeated injections of Compound 48/80, given at intervals of 2–7 days, the gastric secretory response progressively diminished in all animals (Table I). This decreasing effectiveness of Compound 48/80 was not due to a fall in sensitivity of the gastric glands to histamine, since histamine injected subcutaneously still elicited the usual secretion. A condition of complete refractoriness to Compound 48/80 was obtained by decreasing the interval between injections (Fig. 2). Such an animal not only shows no gastric secretory response to Compound 48/80, but

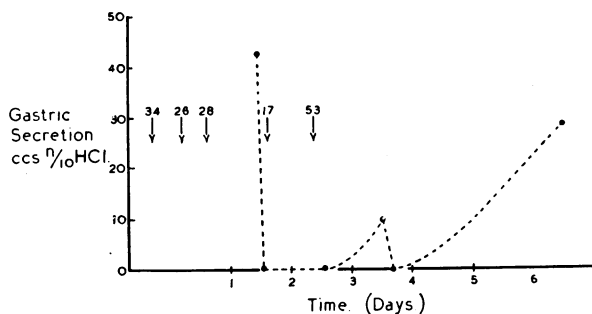


FIG. 2.—Graph of total gastric secretion (c.c. 0.1N-HCl) produced by repeated injections at varying intervals of 10 mg. Compound 48/80. Inserted figures are gastric secretory responses (c.c. 0.1N-HCl) to 1 mg. histamine acid phosphate at times marked by accompanying arrows.

facial swelling and signs of itchiness are also completely absent. This was repeatedly obtainable in two dogs in which it was attempted. This refractoriness does not, however, involve the secretory response to histamine; for instance in Fig. 2 on the second day a gastric secretion of 53 c.c. 0.1N-HCl was obtained with 1 mg. histamine acid phosphate, although immediately afterwards 10 mg. Compound 48/80 failed to elicit any secretion at all. Responsiveness to Compound 48/80, however, is partially restored after 1–2 days (Fig. 2).

DISCUSSION

The inability of mepyramine to influence the actual release of histamine, while largely eliminating signs and symptoms due to injected or released histamine, is of interest for the interpretation of the mechanism of action of antihistamine drugs in clinical conditions where histamine release is involved. Our experiments suggest

that the therapeutic usefulness of these drugs under such circumstances may lie entirely in their ability to interfere with actions of histamine subsequent to its release, whereas the release itself is not interfered with.

The remarkable phenomenon of temporary complete refractoriness to a histamine liberator merits further investigation. For example, it would be of interest to know whether or not protection against a liberator such as Compound 48/80 confers resistance to other conditions associated with histamine release. In this way it might prove possible to determine whether histamine is liberated by different mechanisms under different conditions. Our experiments do not distinguish the possible processes involved in this refractoriness, such as the decrease in available histamine, a reduced "sensitivity" of the tissues, or the development of protective autacoid mechanisms.

SUMMARY

The histamine liberator Compound 48/80 is capable of releasing large amounts of histamine in the unanaesthetized dog. Although signs associated with histamine release, such as facial swelling and itchiness, are almost completely eliminated by mepyramine, the amount of histamine released, as determined by the amount of gastric secretion, is not reduced.

Repeated administration of Compound 48/80 produces a temporary state of complete refractoriness to the same dose of the drug.

REFERENCES

- Baltzly, R., Buck, J. S., de Beer, E. J., and Webb, F. J. (1949). *J. Amer. chem. Soc.*, **71**, 1301.
Feldberg, W. (1941). *Ann. Rev. Physiol.*, **3**, 671.
Grossman, M., and Robertson, C. R. (1948). *Proc. Soc. exp. Biol., N.Y.*, **68**, 550.
Krantz, J. C., Carr, C. J., Bird, J. G., and Cook, S. (1948). *J. Pharmacol.*, **93**, 188.
Lourie, E. M., and York, W. (1939). *Ann. trop. Med. Parasit.*, **33**, 289.
MacIntosh, F. C., and Paton, W. D. M. (1949). *J. Physiol.*, **109**, 190.
Paton, W. D. M. (1951). *Brit. J. Pharmacol.*, **6**, 499.
Reuse, J. J. (1948). *Brit. J. Pharmacol.*, **3**, 174.
Ricketts, W. E., Kirsner, J. B., and Palmer, W. L. (1949). *Amer. J. med. Sci.*, **217**, 539.
Schild, H. O. (1947). *Brit. J. Pharmacol.*, **2**, 189.
Staub, H. (1946). *Helv. physiol. pharmacol. Acta*, **4**, 539.
Wells, J. A., Morris, H. C., and Dragstedt, C. A. (1946). *Proc. Soc. exp. Biol., N.Y.*, **61**, 104.
Woodward, E. R., Dragstedt, L. R., Tovee, E. G., Oberhelman, H. A., and Neal, W. B. (1948). *Proc. Soc. exp. Biol., N.Y.*, **67**, 350.