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OBSERVATIONS ON HISTAMINE-INDUCED PRURITUS AND PAIN

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In the course of previous experimental work (Bain, Broadbent, and Warin, 1949) it was noticed that intradermal injections of histamine dissolved in normal saline usually caused pain, but that itching was unusual. These results agreed fairly well with those of Rosenthal and Minard (1939). On the other hand, Melton and Shelley (1950) reported that, although histamine in normal saline did not often produce itching, pruritus was frequent if the saline was buffered. Lewis (1942), however, claimed that itching was predominant even with normal saline as the vehicle. There is, moreover, evidence that itching is common when histamine solutions are applied to the scarified skin (Lewis, 1942; Broadbent, 1953); and, as histamine, present in the skin in an inactive form, may in some circumstances be released to cause itching (Broadbent, 1953), further investigation seemed desirable.

The present paper confirms that the nature of the vehicle in which the histamine is dissolved, and the way in which it is introduced into the skin, are factors in determining the type of skin sensation produced by exogenous histamine.

METHODS

Histamine acid phosphate was used in all experiments, but the concentrations of histamine are referred to in terms of the base.

Vaccine bottles, containing known quantities of either normal or of buffered saline, were sterilized in an autoclave. The buffered saline had the following composition: NaCl 8.5 g., NaH_2PO_4 0.576 g., Na_2HPO_4 2.5 g., distilled water to one litre.

Histamine solutions used in the experiments were prepared by injecting appropriate volumes of a sterilized stock solution of histamine into the vaccine bottles, with aseptic precautions.

The various solutions used had the following *p*H values, as determined by a glass-electrode *p*H meter accurate to 0.2 of a unit: normal saline, 5.8; buffered saline, 6.8; normal saline with histamine 2 μg./0.1 ml., 5.3; buffered saline with histamine 2 μg./0.1 ml., 7.1; buffered saline with histamine 3 μg./0.1 ml., 7.0. Intradermal injections (0.1 ml.) were made with tuberculin syringes fitted with fine (26 Ga.) hypodermic needles, and scarifications were effected with a sterilized needle. The injections and the scarifications were both performed on the skin of the middle third of the ventral aspects of the forearms. Comparisons were made by applying one solution to the left, and the other to the right, forearm. A short interval, between inserting the needle and injecting the solution, allowed for the subsidence of the pain produced by the introduction of the needle. Scarification was effected by making three parallel scratches through 0.1 ml. of the histamine solution, and then a further three scratches crossing the first series at right angles. The total area of skin affected was about 1 cm.^{2} With the exception of J. L. B. and B. R. (both of European origin) all subjects were Nigerian medical students. In each experiment the subjects were asked to note the time at which the two solutions were applied to the skin, the type of sensation which ensued—pain or itching—and the time when the sensation ceased. In the experiment, the results of which are detailed in Table I, subjects were, in addition, asked to note which injection was the more painful.

TABLE I

COMPARISON OF THE SENSATIONS PRODUCED BY THE INTRADERMAL INJECTION OF HISTAMINE (2 μG. IN 0.1 ML.) IN NORMAL SALINE AND IN BUFFERED SALINE

Subject	Normal Saline		Buffered Saline	
	Duration (min.) of Itch	Pain	Itch	Pain
J. J. E.	0·0	d.i.	6·0	6·0
I. O. N. N.	0·0	d.i.*	4·0	d.i.
H. N. O.	0·0	,,	9·0	,,
F. G. A. M.	2·0	,,	12·0	,,
S. M.	0·0	0·5*	5·0	,,
U. S.	7·0	4·0*	15·0	,,
W. I. B. O.	0·0	6·0*	12·0	,,
E. V. J. K.	0·0	d.i.	0·5	3·0
C. G. C.	0·0	d.i.*	2·0	1·0
E. A. B.	0·0	0·5*	0·0	d.i.
E. U. A.	0·0	d.i.*	0·5	,,
B. O. F.	5·0	,,	0·0	,,
A. O. O.	5·0	,,	0·0	,,
A. E. I.	1·0	1·0	8·0	2·0
B. R.	1·0	d.i.*	4·5	0·0
C. A. I.	0·0	d.i.	2·5	1·0
R. B. A.	0·0	2·5*	10·0	d.i.
Mean	1·23	0·85	5·35	0·77
S.E.	±0·52		±1·18	

* Denotes that the normal saline injection was more painful than the buffered saline injection.

d.i. = pain during the period of injection only.

Results

A comparison of the sensations produced by the intradermal injection of 2 μg. histamine in 0.1 ml. normal saline, and in 0.1 ml. buffered saline, respectively, is shown in Table I. It is evident from this Table that histamine dissolved in buffered saline produces a greater incidence and duration of itching ($P<0.05$), but less pain than does histamine dissolved in normal saline. A comparison of the sensations produced by intradermal injection of 0.1 ml. of each of the vehicles alone is shown in Table II. The buffered saline does not cause appreciably more itching than the normal saline.

TABLE II

COMPARISON OF THE SKIN SENSATIONS PRODUCED BY THE INTRADERMAL INJECTION OF 0.1 ML. NORMAL SALINE AND OF 0.1 ML. BUFFERED SALINE

Subject	Normal Saline		Buffered Saline	
	Duration (min.) of Itch	Pain	Itch	Pain
R. B. A.	0·0	0·2	0·0	2·0
C. A. I.	0·1	d.i.	0·0	d.i.
L. E. O.	0·0	0·5	0·0	1·3
E. A. I.	1·0	0·0	3·0	1·0
E. A. M.	0·0	0·5	0·0	0·5
B. I. N.	0·0	0·0	0·0	2·0
J. L. B.	0·0	0·1	0·0	0·0
B. R.	0·2	0·0	0·0	0·0
E. F. E.	0·0	0·0	0·0	1·0
S. V. E.	0·0	0·0	0·0	2·0
E. I. E.	1·5	0·0	1·0	0·0
Mean	0·25	0·12	0·36	0·89

d.i.=pain during the period of injection only.

TABLE III

COMPARISON OF THE SENSATIONS PRODUCED BY 3 μG. HISTAMINE IN 0.1 ML. BUFFERED SALINE, WHEN INJECTED INTRADERMALLY AND WHEN APPLIED TO THE SCARIFIED SKIN

Subject	Intradermal Injection		Scarification	
	Duration (min.) of Itch	Pain	Itch	Pain
G. O. S.	2·0	d.i.	9·5	0·0
G. A. ..	2·0	0·0	10·0	0·0
E. F. B.	4·0	2·0	9·0	0·0
A. I.	6·0	1·0	22·0	0·0
A. O. A.	1·0	3·0	9·0	0·0
U. J. E.	0·0	3·0	12·0	0·0
N. O. H. O. ..	0·0	3·0	19·0	0·0
J. L. B.	0·0	0·5	2·0	0·0
E. O. I.	13·0	0·0	9·0	0·0
E. I. E.	0·0	d.i.	7·0	1·0
E. A. E.	6·0	2·0	9·0	0·0
L. E. O.	0·0	2·0	13·0	0·0
C. A. I.	2·0	0·0	9·0	0·0
R. B. A.	8·0	d.i.	11·5	0·0
Mean	3·14	1·18	10·79	0·1
S.E.	±1·03		±1·30	

d.i.=pain during the period of injection only.

A comparison of the sensations produced by 3 μg. histamine in 0.1 ml. buffered saline when injected intradermally and when applied to the scarified skin is shown in Table III. It is clear that application to the scarified skin causes a higher incidence and a far greater duration of itching ($P<0.001$), but a lesser incidence of pain, than does intradermal injection.

Discussion

When histamine in normal saline is injected intradermally itching occurs infrequently, but pain is common (Table I). This confirms previous observations (Rosenthal and Minard, 1939; Broadbent, 1953). When histamine is dissolved in buffered saline, both the incidence and duration of itching are increased, thus supporting the observations of Melton and Shelley (1950). As injections of buffered saline alone are not more pruritic than those of normal saline (Table II), the difference may possibly be due to the more painful character of the injections of histamine in normal saline, since pain can inhibit the appearance of itch (Graham, Goodell, and Wolff, 1951). The solutions of histamine in normal saline are more acid than those of histamine in buffered saline.

That histamine in buffer solution is far more pruritic when applied to the scarified skin than when injected intradermally is all the more striking, as nearly all of the histamine solution applied to the scarified skin is seen to stay on the skin surface, and only a minute portion can reach nerve endings, whereas when a similar volume of solution is injected intradermally all the histamine eventually comes into contact with the surrounding tissues. There are several possible explanations of this observation. It may be (1) that dermal oedema interferes with itching (Cormia and Kuykendall, 1953), (2) that pain attending the intradermal injection inhibits the pruritus (Graham, Goodell, and Wolff, 1951), or (3) that the nerve endings subserving the itch sensation lie in the basal layers of the epidermis and are therefore superficial to the injection site (Broadbent, 1953). Such nerve endings would be exposed by scarification of the skin.

It is interesting that the application of histamine to the scarified skin produces lesions resembling those which occur in urticaria in that itching is prominent, whereas itching may be completely absent following the intradermal injection of histamine even when buffered saline is used as the vehicle. Itching is usually absent, but not always so, in dermographism.

SUMMARY

1. Intradermal injections of histamine dissolved in normal saline commonly cause pain. Itching is infrequent.

2. Intradermal injections of histamine dissolved in a special buffered saline cause a greater incidence and duration of itch than do injections of histamine dissolved in normal saline.

3. Intradermal injections of buffered saline alone are not appreciably more pruritic than those of normal saline.

4. When applied to the scarified skin histamine dissolved in the buffered saline causes a greater incidence, and a far greater duration, of itching (but less pain), than when injected intradermally.

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