

INFLUENCE OF ANTIHISTAMINES, SEDATIVES, AND ASPIRIN ON EXPERIMENTAL ITCH

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Abstract. Experimental itch was elicited in volunteer patients by i.c. injection of histamine, trypsin (a protease-releasing histamine) and papain (a protease not releasing histamine); itch duration and flare size were measured. The patients then received chlorcyclizine (an antihistamine with mild sedative effects), levomepromazine (an antihistamine with strong sedative effects), diazepam (a sedative without antihistamine action), aspirin (analgetic and anti-inflammatory agent) or placebo, and experimental itch was again measured. It was found that the two antihistamines reduced the itch and the flare appearing after injection of histamine and trypsin; there was no difference between the two drugs in this respect, though levomepromazine caused marked sedation in contrast to chlorcyclizine. Papain produced no flare and the itch was not significantly altered by antihistamines. Diazepam did not reduce the itch produced by any agent. Aspirin increased the flare and tended to prolong the itch caused by histamine and trypsin. It is concluded that antihistamines inhibit histamine-mediated itch but have no general antipruritic effect, and that sedatives (antihistamines or others) do not decrease experimental itch. Aspirin renders skin more sensitive to histamine; the reason for this is unknown.

There are many effective analgetics, but seemingly no drugs with a general antipruritic effect. Antihistaminics alleviate the symptoms of urticaria but their therapeutic value in other itchy conditions is doubtful and may be due to their sedative properties. Whether analgetic drugs relieve itch is unclear; narcotics even seem to aggravate it.

The intracutaneous injection of histamine or proteases elicits itch and may be used as an experimental model for itch studies (5, 6, 15, 17, 19). It is also postulated that these agents are involved as mediators in various itching conditions. Histamine was initially believed to be the main chemical mediator of itch (4) but proteases are now considered to be the key agents (1, 19).

However, the interrelationship between proteases and histamine is not clear, since some proteases, e.g. trypsin, release histamine from dermal mast cells and their itch-producing effect may thus, to some extent, be mediated by histamine (2, 9).

In the present paper experimental itch was produced by the injection of histamine, trypsin and the non-histamine-releasing protease papain (2, 9). The aim was to find out whether antihistaminics not only relieve histamine-mediated itch but also have a general antipruritic effect and reduce non-histamine-elicited itch; whether the sedation caused by antihistaminics contributes to relieve itch was also investigated. Finally, the antipruritic effect of an analgetic and anti-inflammatory agent, viz. aspirin, was studied.

MATERIAL AND METHODS

Itch was elicited in volunteer patients treated in the dermatological wards for various dermatoses. Only those were selected who had no lesions on the upper arms interfering with the itch test and who were not being treated with antihistamines, sedatives or salicylates; furthermore the patients should be mentally alert and not more than 50 years old. A few per cent of the patients did not feel itch in preliminary tests and were excluded.

About 0.02 ml of the itch-producing solutions—histamine, trypsin and papain—was injected intracutaneously in the upper arms. The time intervals until itch appeared and disappeared were recorded and the duration of the itch was calculated. When itch was elicited by histamine and trypsin the size of the erythema ("flare") was measured 5 minutes after the injection. The contours of the flare were marked on the skin, then traced on a transparent plastic film and the area measured with the aid of transparent graph paper.

Prior to administering the drugs, itch duration and flare were recorded. The patient then received three tablets: the first to be taken at 3 p.m., the second at bedtime (9-11 p.m.), and the third on the next day about

Table I. Itch duration and flare before and after administration of drugs

Exp. series	Treatment	Trypsin			
		Itch duration (sec)		Flare (mm ²)	
		Before	After	Before	After
I	Chlorcyclizine (n = 18)	105 ± 18	49 ± 10***	601 ± 91	207 ± 40***
	Placebo (n = 16)	89 ± 14	89 ± 14	933 ± 84	945 ± 72
II	Chlorcyclizine (n = 18) Placebo (n = 19)				
III	Levomepromazine (n = 19)	87 ± 13	35 ± 7***	537 ± 85	150 ± 30***
	Placebo (n = 19)	92 ± 14	92 ± 15	703 ± 87	786 ± 86
IV	Diazepam (n = 19)	84 ± 14	90 ± 13	752 ± 96	774 ± 82
	Placebo (n = 20)	95 ± 12	94 ± 13	858 ± 70	960 ± 81
V	Aspirin (n = 20)	67 ± 9	74 ± 9	555 ± 83	712 ± 86** ^a
	Placebo (n = 20)	95 ± 12	94 ± 12	652 ± 82	676 ± 78
Mean		89 (n = 151)		702 (n = 151)	

Mean values ± S.E.M.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

^a Increased value after drug administration.

3 hours before the itch test. (In the aspirin series the patients received six tablets and took two tablets each time.) Both the patient and the assistant who made the injections and recordings were ignorant of what kind of tablets had been given. In all series the patients were randomly divided into two equally large groups; one group received placebo, the other the active drug.

The itch-producing agents were dissolved in saline—trypsin (Trypure, Novo Industri, Copenhagen, Denmark) at a concentration of 100 µg/ml; papain (2 × crystallized, Sigma Chemical Co, St Louis, Miss., USA) 50 µg/ml; histamine dihydrochloride, 10 µg/ml.

The following drugs were used: chlorcyclizine, 50 mg coated tablets (Di-Paralene®, Abbott Laboratories, North Chicago, Ill.), levomepromazine, 5 mg coated tablets (Nozitan®, AB Leo, Hälsingborg, Sweden), diazepam, 5 mg tablets (Valium®, Hoffman-LaRoche & Co AG, Basle, Switzerland) and aspirin (acetylsalicylic acid), 0.5 mg tablets (Magnecyl®, ACO Läkemedel, Solna, Sweden).

RESULTS

I.c. injection of 2 µg trypsin (0.02 ml of a solution containing 100 µg/ml) produced an itch sensation at the injection site lasting for 89 sec and flare of 702 mm² in 151 determinations. Itch duration and flare caused by histamine 0.2 µg were 122 sec and 961 mm² in 188 determinations. Papain produced no flare and only itch duration was measured; the mean time was 131 sec in 114 determinations (Table I, last line).

After administration of chlorcyclizine—an antihistamine with very weak sedative effects—the

mean itch duration and flare caused by trypsin and histamine decreased significantly, from 105 to 49 and 158 to 36 sec, respectively (Table I, Series I). Actually the trypsin itch disappeared completely (itch duration 0 sec) in 17% of the subjects and histamine itch completely in 56%. Many of those who still felt itch reported that the feeling of itch was reduced after chlorcyclizine. Papain itch, on the other hand, was not altered significantly by giving the patients chlorcyclizine (Table I, Series II).

Levomepromazine—an antihistamine with pronounced sedative effects—had a similar influence as chlorcyclizine on histamine and trypsin itch and flare. The papain itch was not significantly reduced (Table I, Series III).

Diazepam, which has sedative properties but no antihistaminic action, did not influence the itch duration and flares induced by any of the solutions (Table I, Series IV).

When patients had been given aspirin the duration of itch caused by histamine and trypsin tended to increase and the flare size became larger (Table I, Series V). Papain was not given in these experiments.

Placebo tablets did not significantly alter itch duration and flare in any of experimental series.

In Fig. 1 the itch duration and flare after the drugs are expressed as a percentage of the values obtained before drug administration. It is seen

Histamine				Papain	
Itch duration (sec)		Flare (mm ²)		Itch duration (sec)	
Before	After	Before	After	Before	After
158 ± 30	36 ± 12***	937 ± 124	409 ± 56***		
134 ± 24	144 ± 26	1 207 ± 91	1 236 ± 92		
124 ± 25	34 ± 9***	960 ± 144	512 ± 96***	151 ± 34	114 ± 28
154 ± 22	161 ± 27	937 ± 103	1 009 ± 118	171 ± 20	176 ± 34
105 ± 14	29 ± 8***	885 ± 120	285 ± 63***	119 ± 38	70 ± 51
94 ± 14	96 ± 14	945 ± 103	1 016 ± 98	91 ± 21	109 ± 34
116 ± 20	124 ± 21	893 ± 102	853 ± 86	115 ± 25	120 ± 28
134 ± 21	141 ± 22	1 047 ± 94	1 154 ± 98	142 ± 23	148 ± 32
91 ± 12	103 ± 15* ^a	920 ± 86	1 057 ± 87* ^a		
116 ± 17	122 ± 19	925 ± 86	957 ± 91		
122 (n = 188)		961 (n = 188)		131 (n = 114)	

that trypsin itch is decreased to about the same extent after both chlorcyclizine and levomepromazine and that the same is true of flare (Fig. 1a). Also, the histamine responses were similarly suppressed by chlorcyclizine and levomepromazine (Fig. 1b). When comparing Fig. 1a and 1b it is noted that of the trypsin responses flare is more suppressed than itch by both antihistamines, whereas these relations are reversed in the histamine responses. However, these differences are not statistically significant.

The patients were asked about their subjective feelings concerning the tablets. Chlorcyclizine and placebo had a sedative effect in a few patients, while levomepromazine and diazepam made most patients feel tired or sleepy (Table II).

DISCUSSION

In the present investigation experimental itch was elicited with histamine and proteolytic enzymes, agents which are considered to be peripheral mediators of pathologic itch and are probably released or activated in various pruritic diseases (1, 2, 4, 19). The advantage of studying experimental itch is that conditions are more easily controlled than in clinical itch. The disadvantage is of course that not all circumstances correspond to those of the clinical situation.

As a measure of itch we used the itch duration. Another possibility would have been to determine the itch threshold, i.e. the lowest itch-eliciting concentration of the histamine and protease so-

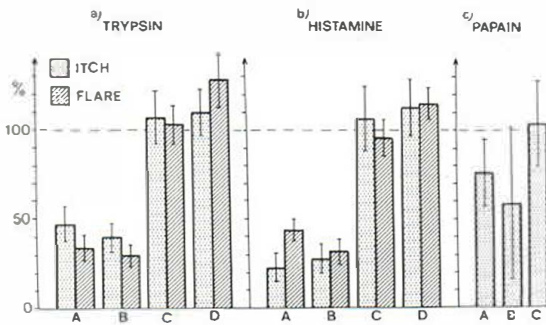


Fig. 1. Itch duration and flare after drugs, expressed as per cent of the values obtained before drug administration. A, Chlorcyclizine (Di-Paralene®); B, levomepromazine (Nozinan®); C, diazepam (Valium®); D, aspirin (Magnecyl®).

Table II. Sedative effect of the administered drugs

Exp. ser.	Treatment	Total no. of subjects	No. of patients reporting sedation			
			0	+	++	+++
I	Chlorcyclizine	18	14	1	3	
	Placebo	16	13	1	2	
II	Chlorcyclizine	18	11	2	5	
	Placebo	19	15	1	3	
III	Levomepromazine	19	6	1	9	3
	Placebo	19	16	1	2	
IV	Diazepam	18	5	3	11	
	Placebo	20	16	1	3	

0 = no sedation, + = slightly tired, ++ = tired or sleepy, +++ = very sleepy.

lutions. However, itch duration is considered to be a somewhat more accurate measure than itch threshold (17). The histamine effect was measured by recording the size of the axon-mediated erythema, the flare.

Antihistaminics are used not only in treating urticaria but also in other itching diseases, where the role of histamine is not clear. In many uncontrolled and a few controlled studies (10, 12, 20) favourable effects of antihistaminics have been found. Other authors have found that the antipruritic effects of antihistamines do not differ from those of placebo (7, 13). These contradictory results may have several explanations, one of which might be that different diseases have been studied: those who have found antihistaminics to have a good effect have studied diseases where histamine mediates the itch; those who have not found antihistamines effective may have studied diseases where histamine is not involved (13). The favourable clinical effect of antihistaminics found by some investigators could also be explained if antihistaminics have an antipruritic effect not connected to their histamine-antagonistic property; possibly it might simply be due to the fact that most antihistaminics are, at the same time, sedatives. In a comparative trial of an antihistaminic and a barbiturate in pruritus there was no significant preference for either drug (8).

In the dosage used in the present study chlorcyclizine and levomepromazine caused approximately the same reduction of flare sizes, i.e. they had similar antihistaminic effects. Also, the itch-reducing effects were similar, though levomepromazine caused marked sedation while chlorcyclizine did not. This implies that the sedative component has no significance in relieving itch. Diazepam which is a sedative without antihistaminic properties affected neither itch nor flare.

The papain-produced itch differed somewhat from that elicited with histamine and trypsin. Many patients stated that papain itch had a more pricking character. In agreement with previous observations (1, 2, 9), it was also found that the vascular reactions—redness, weal and flare—which are seen when histamine acts on skin, did not appear, i.e. papain did not seem to release histamine from dermal mast cells. Whereas the itch caused by histamine and trypsin did not vary much between the individuals and was fairly constant from one day to another in the same

individual (16) (provided antihistamines had not been given), the papain itch varied more. Accordingly the standard errors of the papain experiments were higher and no statistically significant reduction of papain itch after administration of the drugs could be demonstrated. These findings support the conclusion that antihistamines do not have a general antipruritic effect and that the papain itch is not mediated by histamine.

The present experiments may also lead to some considerations of the itch-eliciting action of trypsin. According to Arthur & Shelley (1, 2, 19) all endopeptidases produce itch after intracutaneous injection, irrespective of whether they release histamine from cutaneous mast cells or not. On the other hand, trypsin seems to produce itch mainly by releasing histamine: trypsin does not cause itch in subjects who fail to itch after intracutaneous injection of histamine (2); depletion of the local histamine stores by pretreatment with the histamine liberator compound 48/80 reduces the trypsin itch markedly (9). If trypsin had an itch-producing effect of its own beyond that caused by histamine, antihistamines would reduce the flare more than the itch. Such a tendency, though not statistically significant, was found in the present study: chlorcyclizine reduced itch to 47% and flare to 36%; levomepromazine reduced itch to 40% and flare to 30%. The tendency of the histamine responses was reversed: chlorcyclizine reduced itch to 23% and flare to 44%; levomepromazine to 28 and 32% respectively. However, the differences are small and no definite conclusions can be drawn. In any case, a great deal of trypsin itch seems to be mediated by histamine released from dermal mast cells.

Sedating of the patients did not decrease the itch response in these experiments. However, it is important to bear in mind that these results are obtained by studying experimental itch and it must not be concluded that sedatives are without therapeutic value in treating clinical itch. Naturally it is important that patients with pruritus have the opportunity to obtain adequate sedation during the night, not least in an attempt to decrease the scratching and thus the vicious itch-scratch cycle.

Itch and pain have many similarities. Some of the agents which produce itch when acting on the superficial neuroreceptors, elicit pain on deeper stimulation: both pain and itch are conducted

in the fine unmyelinated C-fibres (19, 21) and along the lateral spinothalamic tract to thalamus. Patients who are unable to feel pain because of injury or congenital defect, are also unable to feel itch (3, 11). Against this background it was considered of interest to study the influence of an analgetic, acetylsalicylic acid, on experimental itch. However, it turned out that aspirin increased the flare induced by histamine and trypsin, and also tended to increase the itch induced by histamine. Moore-Robinson & Warin (14) made a similar observation when studying the effect of aspirin on patients with urticaria. They found that 22% of patients with chronic urticaria became worse by taking aspirin. A few of these patients were given i.c. injections of histamine and it was found that the histamine weals were significantly larger after aspirin. It is also a general clinical experience that aspirin seems to have an exacerbating effect on urticaria. It has been suggested that aspirin is a histamine liberator but this seems unlikely since most histamine liberators are bases (15), while aspirin is an acid. In the present experiments acetylsalicylic acid somehow made the skin more sensitive to histamine, but the mechanism for this action is unknown. One explanation could be that acetylsalicylic acid might inhibit histamine catabolism.

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