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EVALUATION OF DRUG INFLUENCE ON THE ITCH DURATION IN THE SKIN OF PATIENTS WITH ATOPIC DERMATITIS, VARIOUS ECZEMAS AND PSORIASIS

I. Experiments in involved skin. Comparison with itch threshold technique

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In a previous report (8) it was shown that in the involved skin of patients with atopic dermatitis (prurigo Besnier) various eczemas and psoriasis the itch duration values were constant in about three-quarters of the cases in investigations repeated daily during three days or at intervals of one week or two weeks and—in recurrent cases—within one to four months. Itch duration was estimated by trypsin intracutaneous method elaborated by the author (7, 8). The further question arising in this connection is the influence of an antipruritic drug on the itch duration as well as the comparison of this method with the other usual experimental technique, i.e. the estimation of itch threshold.

I. Influence of antihistamine on itch duration in the affected skin of patients with atopic dermatitis, eczemas of various forms or psoriasis

1. *Influence of irregular antihistamine administration*

Material and methods. Itch duration was estimated in 16 patients with atopic dermatitis, eczema of different varieties or psoriasis. During their hospital stay the patients were given antihistamine irregularly when the pruritus was severe. In 12 patients this was done at intervals of one–two–three days, and in all patients after an interval of one week.

Itch duration was estimated by intracutaneous administration of fresh solutions of crystalline trypsin stabilized with 4 % calcium chloride and diluted with physiologic saline. Trypsin, 1:10,000, was given strictly superficially in a dose of 0.02–0.03 ml (tuberculin syringe and needle No. 20). It was applied to the affected skin of the overarms at no less than two sites and the mean itch duration was recorded.

Different affected areas of the overarms were chosen for these experiments and for those in which injections were repeated to avoid possible local "exhaustion" of the same inflamed area. The concentration of 1:10,000 was chosen, in accordance with previous tests, as required for eliciting itch. All investigations were carried out in the same room at fairly constant temperature, moderate humidity, at same time of day and by the same investigator. The patients were asked to observe their sensation of itch, but no information was given about the quality or concentration of the solution or of the saline used. Patients who were not alert or who reacted to physiologic saline, as well as those under 16 or over 60 were excluded from the investigations. The source of error was taken to be 20 per cent, since itching remains highly subjective even

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Table 1. *Itch duration in involved skin during irregularly given antihistaminics*

Case	Skin disease	Itch duration estimations in intervals of	
		1-2-3 days	1 week
1	Atopic dermatitis	c	c
2	„ „	d	c
3	„ „	c	c
4	„ „		c
5	„ „		c
6	„ „		c
7	Eczema	c	d
8	„	c	c
9	„	c	c
10	„	d	d
11	„		c
12	„	c	d
13	„	c	d
14	Psoriasis	c	c
15	„	d	d
16	„	c	c
16		9: c 3: d	11: c 5: d

c: congruent (unchanged) values
d: discordant values

when assessed by relatively objective methods.

During a period of three days or one week these 16 patients were given, at irregular intervals, the following antihistamines: methdilazine,[1] levomepromazine[2] or promethazine.[3]

Results. Table 1 shows the results of these experiments. Similar itch-duration values were obtained in nine of the 12 patients where estimates were made daily for a period of three days, and in eleven of the 16 patients where the estimates were made weekly. This indicates the similarity of the itch-duration mentioned in the introduction, i.e. about three-quarters of the patients. Thus the antihistaminics which were irregularly given did not cause any essential modification in the itch-duration values in the affected ("itchy") skin of the patients.

[1] Tacaryl®. [2] Nozinan®.
[3] Lergigan®.
[4] Supplied by the kindness of UCB Nordiska AB.

2. *Influence of antihistamine administration*

Material and methods. In 20 patients suffering from the above-mentioned itchy dermatoses and actual pruritus, the itch-duration values were recorded before starting the experiments. A new antipruritic agent was used for the first time: 1[2(p-chlorbenzhydryloxy) ethyl]-4[2(2-hydroxyethoxy)ethyl] piperazine bihydrochloride (UCB, 1486 in tablets à 10 mg)[4] applying double blind technique. In more than half of the cases placebo tablets were given over a period of three days, and itch duration was estimated on the fourth day. During the next three days the UCB tablets were administered, and itch duration was again estimated on the eighth day. The remaining patients received A tablets first and B tablets subsequently. (A=UCB 1486 10 mg, B=placebo.)

Results. Table 2 shows the itch-duration values in the left columns. It is evident that itch duration was diminished in 10 of the 20 patients when comparing the effect of the antihistaminic agent with that of the placebo. The latter influenced the initial control values as follows: 6 diminished, 11 unchanged, and 3 increased. If the antihistaminic effect is compared with the initial, control values in 13 patients itch duration was diminished, and in 7 it remained unchanged.

Comments. The results shown in table 2 indicate that the regular administration of a new antihistaminic (UCB 1485) during a period of three days modified the itch-duration in half of the patients. This number of patients may not appear high but the findings are nonetheless suggestive, if the following are taken into consideration: a) the relatively high constancy of itch-duration values in the affected skin of the patients and, b) the failure of other antihistaminics, administered irregularly, to influence itch duration. The number of patients selected, and the conclusion that reactivity to a drug in half the patients investigated may be regarded as significance,

Table 2. *Itch duration and threshold in involved skin during UCB 1486 and placebo*

Case	Skin disease	Itch duration estimations			Itch threshold estimations		
		UCB-P	UCB-C	P-C	UCB-P	UCB-C	P-C
1	Atopic dermatitis	o	o	o	—	—	o
2	„ „	o	—	—	—	—	o
3	„ „	—	—	+	—	—	+
4	„ „	—	—	—	o	o	o
5	„ „	—	—	o	—	—	+
6	„ „	—	—	o	—	—	+
7	„ „	o	o	o	o	o	o
8	„ „	o	o	o	o	o	+
9	„ „	—	—	o	o	—	o
10	„ „	—	o	o	o	o	o
11	„ „	o	—	—	o	o	o
12	Eczema	—	o	o	—	—	—
13	„	—	—	o	—	—	—
14	„	o	—	—	o	o	o
15	Psoriasis	o	o	o	o	o	o
16	„	o	o	+	o	—	—
17	„	o	—	—	—	—	o
18	„	o	—	—	+	o	—
19	„	—	—	+	—	—	—
20	„	—	—	o	—	o	+
20		10: —	13: —	6: —	10: —	11: —	5: —
		10: o	7: o	11: o	9: o	9: o	10: o
				3: +	1: +		5: +

UCB: UCB 1486 P: placebo C: starting control value
—: diminished itch duration/improved (elevated) itch threshold
o: unchanged
+: increased itch duration/deteriorated (lowered) itch threshold

correspond to observations by other investigators of experimental itch methods (1, 5). The comparison, between placebo and control, or between UCB 1486 and the control in the present series, showed good agreement with the "essential" evaluation, i.e. the effect of the antihistaminic agent compared to that of the placebo.

II. Influence of antihistamine on the itch threshold in the affected skin of patients with atopic dermatitis, eczemas of various forms and psoriasis

1. *Estimation of itch threshold in affected skin, without drug administration*

Since itch duration in affected skin could be influenced to some degree by an antihistamine preparation, it was of interest already from the beginning of the studies to compare this method with the mostly used technique in evaluation of the antipruritic effect of some drugs on experimental itch, i.e. the itch threshold estimation.

Material and methods. The itch threshold was estimated in 15 patients with atopic dermatitis, eczemas of various forms or psoriasis. The following concentrations of trypsin were used: 1:10,000, 1:20,000, 1:40,000, 1:80,000, 1:160,000, and 1:320,000. Thus, the individual itch threshold was measured by increasingly diluted solutions, which were given in irregular sequence, however, and this applied also to the administration of saline, in order to avoid any possible serious sources of error in assessing the patients' sensation of itching.

The threshold was represented by that

Table 3. *Itch threshold in involved skin*

Case	Skin disease	Itch duration estimations in intervals of	
		1-2-3 days	1 week
1	Atopic dermatitis	c	c
2	,, ,,	d	c
3	,, ,,	d	d
4	Eczema	c	c
5	,,	d	c
6	,,	c	c
7	,,	c	c
8	,,	c	c
9	,,	d	d
10	Psoriasis	c	c
11	,,	d	d
12	,,	c	c
13	,,	c	c
14	,,	c	c
15	,,	c	c
15		10: c 5: d	12: c 3: d

c: congruent (unchanged) values
d: discordant values

concentration which, in the judgement of the patients, either failed to elicit itch at all, or caused only an insignificant, uncertain sensation after two applications of the itch elicitor. Otherwise, the technique was the same as that applied in the method used for estimating itch duration, previously described.

The itch threshold of the 15 patients was estimated both daily for three days and after an interval of one week.

Results. Table 3 shows the findings obtained in this investigation. There was similarity in 10 out of 15 cases when daily estimations were made for three days; and in 12 out of 15 cases when estimations were made again after one week.

Comments. Thus, the threshold values for affected skin showed a greater degree of variability than those for itch duration, but, on an average, the threshold values were near to the level of the latter values, i.e. constancy in about three quarters of the patients.

2. *Influence of antihistamine administration*

Material and methods. In the 20 patients, mentioned under I: 2, itch-duration and itch-threshold values were simultaneously estimated at intervals of three days during drug or placebo administration (for details see I: 2).

Results. The results of these tests are shown in the right hand columns in table 2. According to these findings the itch threshold was elevated (i.e. itching diminished) in half of the patients. The placebo had no definite influence on the initial control values.

Comments. In the literature there are relatively few data available in the influence of drugs on experimental pruritus. Cormia & Kuykendall studied the effect of antihistaminics and several other drugs on the itch threshold elicited by histamine application (1), the best effect was obtained when using antihistaminics and an analgetic and the influence of the placebo was 17 per cent in these experiments. Rajka, Korossy & Gozony (5) studied the influence of 78 drugs on morphine-induced experimental itch threshold in a large series, mixing the morphine with the drug investigated. In further experiments, the effect of perorally administered agents on the morphine itch threshold was investigated by the double blind method (6). Shelley & Arthur tested the effect of several systemic preparations on the experimental cowhage itch threshold (9). Kordenszowa & Wiehler (3) performed similar experiments with levomepromazine. The influence of certain topical agents on the experimental itch threshold elicited by the above-mentioned pruritogenic substances, was investigated by several authors (1, 4, 10, 2).

In the present study the influence of the antihistamines investigated agreed with those observed by the itch duration method. To compare these methods for testing of antipruritic agents on a broader basis, including investigations in normal skin as well as clinical evaluation of itching are necessary. Such studies will be reported in a subsequent paper.

SUMMARY

Irregularly given antihistaminics did not influence the experimental itch duration, which according to previous experiments was constant in three quarters of the cases. A new antihistaminic agent 1[2(p-chlorbenzhydryloxy)ethyl]-4[2(2-hydroxyethoxy)ethyl] piperazine bihydrochloride or "UCB 1486", diminished itch duration in half of the patients as compared with the placebo. The same effect was demonstrated on the itch threshold values.

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