A METHOD FOR EVALUATION OF THE INFLUENCE ON EXPERIMENTAL ITCH OF TOPICALLY APPLIED DRUGS

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Many drug preparations for external use—particularly ointments—are considered to have antipruritic effect, but which may not be confirmed by clinical observations. Test methods to evaluate the influence on itch of antipruritic external drugs are rarely used, primarily because of the lack of appropriate techniques. In the available literature there are only five reports on the effect of certain substances on experimental itch. Cormia and Kuykendall (1) studied the effect of topically used EDTA-salts, phenol-menthol-ointment, of a lotion and of saline control on the itch threshold elicited 30 minutes earlier by histamine application. They observed moderate beneficial effects only after EDTA-Na and EDTA-Ca. E. Rajka et al. (5) investigated 11 anti-histaminics, 10 steroids and 4 other externally applied drugs in regard to their effects on itch threshold elicited by morphine 20–30 minutes earlier. Antihistaminics had a better effect in general than steroids and antipruritic effect of over 50% was observed for five preparations. Melton and Shelley (4) found no appreciable effect with 54 topically applied antipruritic preparations on histamine pruritus elicited fifteen minutes later. In a second study series, the test compound was rubbed into the skin immediately after histamine application, with similar negative results. Shelley and Arthur (8) also had totally negative experiences using 12 topical agents in itch, caused by trypsin. Haas (3) applied 27 test substances on the skin followed an hour later by histamine scratch and observed partial inhibition of pruritus by: formalin 1%, menthol 1–2%, phenol 2%, resorcin 5%, thymol 1% as well as of certain topical drugs.

In previous studies the present author found that the duration of itch elicited by intradermally applied trypsin 1 : 10,000 on the upper arm may be used as a test with relatively (in three fourths of the cases) constant values to estimate the influence of oro-nasally administered drugs (6, 7). In the present study the author investigated: (i) if this method is suitable for testing the effect of antipruritic ointments and (ii) the extent of the influence of these topical drugs on itch duration.

Material and Method

Itch duration, as described previously (6, 7), was estimated on the intact skin of the upper arms of patients with itchy dermatoses, particularly those with prurigo Bes-

1 Ethylenediamine tetraacetate-Na.
2 Ethylenediaminetetraacetate Ca.
3 Quotane lotion®.
4 Pragman gel®.
5 Bradex-Vioform creme®.
6 Synopene ointment®.
7 Eurax ointment®.
8 Xylocaine ointment®.
9 Panthesin balsam 5%®.
10 Percainal ointment 5%®.
11 Priscol ointment 10%®.

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Fig. 1. Method of evaluating antipruritic effect of topically applied agents e.g. by testing ointment E on a patient.

* Itch duration after intracutaneously applied trypsin.

Figier and with eczemas of different varieties. The age of the patients was between 16 and 60 years and with few exceptions different persons were used in different tests. Itch duration was determined after two intradermal injections of 0.02-0.03 trypsin 1:10,000, given strictly superficially in the skin of the right and left arms. The test substance or vaseline was then gently rubbed for one minute into a skin area of 4 cm \times 4 cm (which was 2-3 cm distant from the first application area). The excess was immediately washed off with dilute alcohol. After 30 minutes a new estimation of itch duration elicited by a second pair of trypsin injections into the "ointment area" was made. The average itch duration values before and after the application of the ointment or the vaseline were compared (Fig. 1). A double blind technique was used, and the application of the ointment or the vaseline was varied between the right and left upper arm from patient to patient.

Ten ointments in "clinical" concentrations were tested. Eight of these were claimed (2) to have antipruritic effect i.a. steroids and an antihistaminic (the possible side effects of the antihistaminic preparation were not considered in this investigation). Moreover, two topical drugs with anti-inflammatory effect (ointments C and F) were also used. Each of these drugs was first applied in a screening procedure on 10 subjects. The drugs showing antipruritic effect in at least half of the cases were then tested on another 10 patients. The criteria of antipruritic effect were that the itch duration value estimated before applying the test ointment or the vaseline was diminished by more than 20%.
Table 1. The influence of ten ointments on experimental itch

<table>
<thead>
<tr>
<th>Ointment code</th>
<th>Relevant therapeutic indication in relation to itch or inflammation (2)</th>
<th>Antipruritic effect on experimental itch in investigated subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Pruritus vulvae et ani</td>
<td>2/10</td>
</tr>
<tr>
<td>B</td>
<td>Pruritus anogenitalis</td>
<td>3/10</td>
</tr>
<tr>
<td>C</td>
<td>Superficial inflammatory infiltrations</td>
<td>3/10</td>
</tr>
<tr>
<td>D</td>
<td>Pruritus ani</td>
<td>4/10</td>
</tr>
<tr>
<td>E</td>
<td>Various types of pruritus</td>
<td>4/10</td>
</tr>
<tr>
<td>F</td>
<td>(Experimental anti-inflammatory preparation)</td>
<td>4/10</td>
</tr>
<tr>
<td>G</td>
<td>Pruritus senilis, ani et vulvac</td>
<td>5/10 + 4/10 = 9/20</td>
</tr>
<tr>
<td>H</td>
<td>Pruritic dermatoses</td>
<td>5/10 + 5/10 = 10/20</td>
</tr>
<tr>
<td>I</td>
<td>Pruritus anogenitalis</td>
<td>5/10 + 5/10 = 10/20</td>
</tr>
<tr>
<td>J</td>
<td>Pruritus</td>
<td>6/10 + 5/10 = 11/20</td>
</tr>
</tbody>
</table>

Results

The results of the testing are summarized in Table 1. It would seem that one ointment had an antipruritic effect in 11 of 20 cases, two ointments in one half of the cases and another ointment in 9 and 20 cases.

In most cases the results were very similar on the right and left sides and the influence of minor differences observed was negated by the alternating procedure for the application of the ointment and the vaseline. The vaseline effect was considered to be stronger than the effect of the test ointment only in 3 out of 140 experiments.

Discussion

A failure rate of 20% was observed in previous experiments using perorally antihistaminic drugs. In these previous investigations the maximal influence on the itch duration was demonstrated in about 50% of the cases (in 25% of the cases the itch duration values were inconstant (6, 7)). Thus, an effect of the tested substance on the experimental trypsin itch should exceed a quarter of the cases investigated. This was in general also found in present experiments (Table 1). The antipruritic effect of 6 of the tested ointments was, however, rather low whereas 4 ointments decreased the itch duration in about half of the patients.

Since the aim of the present study was to elaborate a suitable method for testing the antipruritic effect of ointments and not the evaluation of some preparations, only codes were used. The therapeutic indications of the ointments tested according to the indications of the register of pharmaceutical preparations in Sweden (2) are given. These indications are probably primarily based on clinical observations since no data revealed by testing experimental itch are known. This may be the reason why the antipruritic effects in spite of very similar indications were rather different. Furthermore, neither of the two ointments with superficial anti-inflammatory effect (one of them being a newer type of experimental preparation) had a convincing effect on experimental itch duration. On the basis of these findings there appears to be real need for experimental evaluation of antipruritic effect of preparations intended for external use instead of accepting generally used empirical statements.

Earlier experimental methods, according to the references cited, were based on the itch sensation (3, 4, 8) or on the effect on the experimental itch threshold (1, 5). In previous and present experiments the itch duration test proved to be a more constant and a relatively simple in vivo technique for evaluation of possible antipruritic effect. Unlike the threshold method, the duration method does not require many trypsin injections, which in themselves influence the results. The present findings evaluating topical antihistaminic agents appears to confirm the usefulness of this method.
SUMMARY
A relatively simple test for the evaluation of antipruritic effect of topically applied drugs is described. The duration of trypsin itch elicited before and after application of 10 ointments was measured on the unaffected skin of the upper arm. Eight of these ointments are designated as antipruritic and two of them as anti-inflammatory, notwithstanding that the test results varied. Three ointments had an antipruritic effect in half or more of the cases. It is emphasized that instead of relying on empirical statements experimental itch test methods should be used to evaluate the antipruritic effect of topical ointments.

REFERENCES
2. FASS (Farmaceutiska specialiteter i Sverige): Register of pharmaceutical specialties in Sweden, Almqvist & Wiksell, Uppsala, 1968.