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Topically Applied Aspirin Rapidly Decreases Histamine-induced Itch

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The effect of topical aspirin and its model vehicle dichloromethane on itch experimentally induced with histamine was studied in 16 subjects, using a visual analogue scale and computerized thermal sensory analyzer (TSA). Following histamine injection aspirin, but not its vehicle, significantly reduced itch duration ($p=0.001$) and decreased itch magnitude as measured with a visual analogue scale ($p<0.04$). Histamine injection caused elevation of warmth sensation threshold ($p=10^{-8}$) but did not affect cold and heat pain thresholds. Aspirin and vehicle application did not affect thermal and pain thresholds during histamine-induced itch. The current data suggest that topical application of aspirin may be beneficial for the treatment of histamine-mediated itch. Its therapeutic role in the management of clinical itch remains to be determined. ***Key words: thermal sensory analyzer; visual analogue scale.***

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Prostaglandins play an important role in pain and itch (1, 2). The mechanism of action of aspirin as an analgesic is based on its inhibition of prostanoid biosynthesis. Prostaglandins cause hyperalgesia by sensitizing the small nerve fiber endings to various mediators; aspirin inhibits this effect (2–4). Since pain and itch are transmitted by these small nerve fibers mainly by C fibers, it is reasonable to assume that aspirin may reduce itch. However, in a large study by Daly & Shuster oral aspirin did not affect itch (5). Hägermark found that oral aspirin may aggravate histamine-induced itch (6). King described excellent results with the topical use of aspirin and chloroform in alleviating pain in post-herpetic neuralgia in a non-controlled study (7). Benedettis et al. (8) performed a controlled trial with aspirin/diethyl ether mixture in the treatment of acute and post-herpetic neuralgia and found it to be highly efficient treatment for both diseases. However, no controlled trials have been conducted with these compounds in the treatment of itch.

Recently we demonstrated that experimentally histamine-induced itch increases warm sensation thresholds, a C fiber-mediated sensation, measured with a computerized thermal testing device (9).

The purpose of the current study was twofold:

1. To study the effect of topical aspirin on magnitude and duration of itch induced experimentally by histamine.
2. To study the effect of this drug on C fibers during experimentally induced itch, utilizing a computerized thermal testing device.

MATERIALS AND METHODS

Sixteen volunteers (8 males and 8 females) with an average age of 43 ± 6 years participated in the study after giving informed consent.

Protocol

The study was divided into two separate sessions 2 days apart.

First session: thermal thresholds for warm sensation, cold pain and heat pain sensations were measured in both forearms with a thermal sensory testing device. Histamine was then injected intradermally, first in one forearm and following completion of testing in the other forearm. Itch magnitude was measured with a visual analogue scale of 10 cm, each minute during 10 min, at the end of which thermal and pain thresholds were again measured. Itch duration was also recorded.

Second session: in a single-blind study, in random order, the aspirin solution was applied to the left forearm and the vehicle alone to the right forearm. Twenty-five minutes later histamine was injected in each forearm. Itch magnitude was measured with a visual analogue scale of 10 cm, each min for 10 min, at the end of which thermal and pain thresholds were measured. Duration of itch was recorded.

All subjects were studied in a controlled room, with a constant room temperature (22°C) and a relative humidity of 40–50%. The subjects were rested for an acclimatization period of 30 min before study.

Aspirin

Three tablets of aspirin 325 mg (acetyl salicylic acid, Bayer, Del Rio, Texas) with 30 cc dichloromethane (methylene chloride, Fisher Scientific, New Jersey) used as a solvent were employed in each subject. The drug was applied in a standardized amount of 3% aspirin (975 mg in 30 cc over 14 cm^2), where the peltier probe was placed on the flexor aspect of the upper forearm. One compound was tested at a time, as previous studies had shown that it was difficult to distinguish between sensations arising from different areas.

Quantitative thermal testing

All thermal tests were performed with a computerized quantitative thermal sensory device, a TSA 2001 (Medoc, Ramat Yishai, Israel) with a large probe measuring 5×2.5 cm. The peltier probe was placed on the flexor aspect of the upper forearm. The method of limits was used where threshold was determined as an average of four successive stimuli, for warmth sensation and three for cold pain and heat pain thresholds. In this method the subject is exposed to a thermal stimulus of changing intensity and asked to indicate the first onset of sensation; a detailed description of the method is found elsewhere (10, 11). Rates of temperature change were 1°C/s for warm sensation and 2°C/s for cold and heat pain.

Histamine induced itch

Itch was experimentally induced with histamine dihydrochloride (Sigma, St Louis, Mo) in a dose of 100 μg dissolved in 1 cc of normal saline. Histamine was injected intradermally in both forearms.

Statistical evaluation

Analysis of variance with repeated measures was used to determine the effect of histamine injection vs baseline measurements and the effect of aspirin and its vehicle, respectively, upon warm sensation, heat pain and cold pain during histamine injections. Two tailed *t*-test

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compared itch duration in aspirin- and vehicle-treated sites and untreated itch site. The Wilcoxon signed rank test was used for pairwise comparisons between the means of aspirin vehicle and baseline itch magnitude measured each minute for the first 10 min post injection of histamine.

RESULTS

Histamine induced itch in all subjects for a mean period of 16.8 ± 11 min. Warmth sensation threshold increased significantly by 1°C after histamine-induced itch from $33.8°C \pm 0.38$ to $34.8°C \pm 0.72$ ($p = 1 \times 10^{-8}$). Heat and cold pain thresholds did not differ from baseline (data not shown).

Aspirin significantly decreased itch duration, from baseline of $16.8 \text{ min} \pm 11$ to $6.0 \text{ min} \pm 6.3$ ($p = 0.001$) and also in comparison to vehicle $17.7 \text{ min} \pm 11$ ($p = 0.001$). Aspirin also decreased itch magnitude at all time points measured ($p < 0.04$) and also in comparison to vehicle ($p < 0.02$) (Fig. 1). The elevated warmth sensation threshold during histamine itch was neither affected by aspirin nor by the vehicle. The thermal pain thresholds did not differ between aspirin- and vehicle-treated sites and the untreated itch site.

DISCUSSION

This study demonstrated that topical administration of aspirin solution significantly alleviated itch induced by histamine. In a previous study it was found that a high-potency topical corticosteroid used similarly did not affect thermal thresholds and pain but significantly decreased itch magnitude and duration (9). Since both corticosteroids and aspirin inhibit the production of prostaglandins, which are operative in the mechanism of pain and itch, and both modalities are transmitted by the C nerve fibers (12), we may assume that their mechanism of action on nerve fibers is similar.

The results of the present study and our previous study (9) have demonstrated that only warm sensation thresholds are altered during histamine – induced itch, whereas thermal pain thresholds are not affected. These results may give some support to the "selectivity theory" of itch perception, which suggests that itch is elicited by a certain subset of C polymodal fibers with specific central connections (12, 13). Fruhstorfer et al. have observed that changes in skin temperature had a marked influence on histamine-induced itch intensity; however, thermal thresholds were not affected by histamine injections

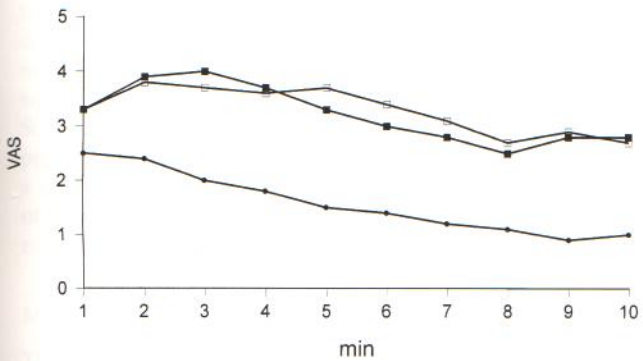

Fig. 1. The effect of aspirin solution (●) vs vehicle (■) and untreated skin (□) on experimentally induced itch, expressed by a 10-cm visual analogue scale. The difference is statistically significant for each time point ($p < 0.04$).

(14). Based on the latter results performed with a non-computerized thermode device they concluded that thermoreceptors do not participate in the generation of itch. Another possibility for the elevated warm sensation threshold after histamine injection is an increase in skin temperature by histamine flare. Kojo & Pertovaara and Kenshalo et al. found that heating the skin produced an elevation of warm sensation thresholds (15, 16).

The mechanism of aspirin effect on itch is not clear. The fact that topical aspirin significantly decreased itch magnitude and duration, while others (5, 6) reported that oral administration of aspirin increases itch duration, must be clarified. A possible explanation for these discrepancies is that topical administration with dichloromethane may have a different effect than the systemic effect. A second explanation is that we do not yet know the oral dose required to inhibit cyclooxygenase activity in the skin. Another explanation may be that the effect of topical aspirin may be different and unrelated to inhibiting cyclooxygenase activity such as blocking receptors of inflammatory mediators and stabilizing neuron membranes or a combination of factors which may desensitize nerve terminals (4, 17). While it remains an open question whether the anti-inflammatory effects of NSAIDs are inseparable from their analgesic actions, at present there are no potent, universally effective topical antagonists of responses to the prostaglandins or leukotrienes. If a combination of aspirin and vehicle which can effectively penetrate the skin inhibits itch, these combinations could be added to the list of effective treatments for pruritus.

Not all of the nociceptive nerve endings are necessarily affected by a specific aspirin-like drug and there can be differences among the different drugs (4). Future studies should evaluate different topical non-steroidal formulas. Another question to be addressed is that of possible systemic adverse reactions with high-dose topical aspirin. The main adverse effect of oral aspirin is gastric irritation. This effect would be minimized using the topical delivery system. The use of this medication would be limited in uremics suffering from pruritus, since NSAIDs impair the renal blood flow. For the present study dichloromethane was chosen as a model solvent on the basis of its solubility, and this was not intended to be a final formulation.

It is of note that the combination of aspirin and dichloromethane tested in this study was found to result in a rapid decrease in itch after a period of only 25 min, indicating that a sufficient quantity of the drug had already achieved a threshold concentration similar to that found with topical corticosteroids.

An intradermal injection of 100 μg histamine is known to be an effective way to induce itch (18) and was therefore chosen for this experimental study. While we have no proof that aspirin solution would be effective in the treatment of clinical pruritus, our results indicate that the topical application of high-dose aspirin in close proximity to cutaneous nociceptors may be highly effective as an anti-pruritic.

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