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INVESTIGATIVE REPORT

Topically Applied Aspirin Decreases Histamine-induced Wheal and Flare Reactions in Normal and SLS-inflamed Skin, but does not Decrease Itch. A Randomized, Double-blind and Placebo-controlled Human Study

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Topically applied aspirin has recently been reported to decrease histamine-induced itch in human volunteers. Our aim is to confirm this and to study the antipruritic ability of topical aspirin in inflamed skin. In 24 non-atopic volunteers, an inflammatory skin reaction was induced in forearm skin at 5 different sites by sodium lauryl sulphate contained in Finn Chambers. Aspirin 10%, aspirin 1%, mepyramine 5% and vehicle were applied to the inflamed and corresponding non-inflamed areas 20 min before itch induction with intradermal histamine injection. Itch and pain were scored on a visual analogue scale at regular intervals. Wheal and flare areas were measured. No difference in itch intensities was found after application of aspirin, mepyramine and vehicle, but more itch was induced in aspirin and mepyramine pretreated sites in inflamed skin compared to normal skin ($p < 0.05$). In normal skin, flare areas were smaller after pretreatment with aspirin 10% ($p < 0.05$) and mepyramine ($p < 0.001$), as were wheal areas after mepyramine ($p < 0.01$), compared to vehicle pretreatments. In inflamed skin, flare areas were smaller after pretreatment with aspirin 10% ($p < 0.01$) and mepyramine ($p < 0.001$), as were wheal areas after aspirin 10% ($p < 0.01$), aspirin 1% ($p < 0.05$) and mepyramine ($p < 0.001$). We conclude that despite a significant skin penetration as measured by the influence on wheal and flare reactions, topically applied aspirin did not decrease histamine-induced itch in the model used.

Key words: acetylsalicylic acid; human model; irritant dermatitis; mepyramine; pruritus; sodium lauryl sulphate; topical treatment.

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Oral medication with aspirin (acetylsalicylic acid) has been reported to reduce the sensation of itch in patients suffering from polycythemia vera (1). Systemic treatment with this drug has hitherto failed to diminish itch in experimental studies (2, 3). In a recent study by Yosipovitch et al., however, topically applied aspirin rapidly decreased histamine-induced itch (4).

Aspirin is an analgesic and can directly influence the pain-eliciting nociceptors when applied topically (5). Aspirin also blocks the cyclo-oxygenase enzyme, thereby inhibiting the formation of inflammatory mediators such as prostaglandins (6). In experimental itch studies, prostaglandin E_1 (7–9), prostaglandin E_2 (1, 10) and prostaglandin H_2 (10) all lowered the threshold to itch inducers such as histamine (7–10), papain (7) and serotonin (1). Thus, theoretically, aspirin and other salicylic compounds could be antipruritic, especially in inflamed skin.

Topical salicylic acid compounds are widely used in dermatology (11). They are relatively non-toxic, although systemic toxicity can occur when large areas of skin are treated (11). They are not recognized as skin sensitizers. The great need for new antipruritic drugs in dermatology makes it important to confirm the observation by Yosipovitch et al. (4).

The primary aim of the present study was to evaluate whether aspirin has an antipruritic effect when applied topically prior to histamine-induced itch. The second aim was to investigate the influence of skin inflammation, induced by sodium lauryl sulphate (SLS) irritant patch test reactions, on the effect of topical salicylate pretreatment. We used our newly developed model (12). The third aim was to investigate whether topically applied aspirin affects the wheal and flare areas after histamine injection in normal and inflamed skin. Topical mepyramine was included in the study as a presumed positive reference (13, 14).

MATERIALS AND METHODS

Study materials

The experiments were performed in November and December 2000 in 12 female and 12 male Caucasian volunteers (aged 22–29 years, mean age 26 years). Inclusion criteria were: age 18–35 years, no past or present history of atopy (i.e. no atopic dermatitis, urticaria, asthma or rhinitis), no past or present

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history of skin diseases or neurological diseases, and no present skin changes on the forearms on examination. Females were not pregnant or lactating, and safe contraception was to be used. No medication or cosmetic creams were allowed during the previous week and no drugs containing corticosteroids or ACTH within 3 months. Informed written consent was obtained from all subjects. The regional ethics committee approved the protocol of the study.

Experimental procedure

On day one, extra large Finn Chambers (18 mm in diameter, filter disc with 150 µl of 1% SLS in distilled water) were applied to the skin of one of the forearms. In both male and female volunteers, chambers were randomly applied to the right ($n = 6$) or left ($n = 6$) volar forearm. To maximize the distance between the chambers, they were applied in a zig-zag pattern. The chambers were removed after 24 h (day two). Sixty minutes after removal of the chambers, skin inflammation was scored using the ESCD guidelines on clinical scoring of acute SLS irritant reactions, simple scoring system (15). Skin redness was measured with a chromameter (Minolta® Chromameter CR 300, aperture 11 mm), and transepidermal water loss (TEWL) was measured using an evaporimeter (Cortex Technology Aps, Hadsund, Denmark). Volunteers were positioned with their forearms shielded by a box, so neither the volunteer nor the interviewer could see the skin reactions. Temperature and air humidity in the room were measured.

Experiments were performed between 8.00 a.m. and 5.00 p.m. Following randomisation, 100 µl of coded antipruritic substance or vehicle was applied to the inflamed test areas and to the corresponding non-inflamed sites on the opposite forearm. Substances or vehicle (100 µl) were applied using 3 × 3 cm hydrocolloid dressing (Duoderm®, ConvaTec) each with an 18 mm diameter central aperture. The dressings were placed on the skin with the hole above the test areas, and test substances were applied to the hole. After 1 min the substances had evaporated and the hydrocolloid dressing was removed from the skin. After a further 20 min, 10 µl of the histamine solution was injected into the dermis of the test areas. The intradermal injections were given centrally in the five inflamed and non-inflamed test areas; each volunteer received a total of 10 intradermal histamine injections. Following injections, the volunteers scored itch intensity originating from the site of injection. Itch intensity was scored after 15 sec, 30 sec, 45 sec and 1 min, and thereafter every minute for 20 min on a 100-mm visual analogue scale, where the left and right end points were marked "no itch" and "maximum itch", respectively. Volunteers were instructed that maximum itch was to be understood as "maximum itch imaginable". To sharpen discrimination between itch and pain, the volunteers were also requested to score pain intensity after 1 min and thereafter every minute for 20 min. Injections were given alternating between the arms, avoiding injections in an area neighbouring the area just injected. The first injection was given in the right arm. At least 80 min passed between injections in adjacent sites. On each forearm, there was a test site that was not pretreated with test substance (the test site closest to the hand). The placebo substance was applied randomly to either the mid-test site or the test site immediately above this test site. Aspirin 10%, aspirin 1% and mepyramine were applied to the test sites according to a randomized Latin-square design.

Five minutes after each injection, the flare area was outlined with a pen on a translucent piece of plastic placed on the forearm skin. Twenty minutes after injection the margin of wheal edema was outlined directly on the skin with a pen. Using tape strip, this was copied to a piece of paper. Wheal and flare areas were then clipped out with scissors and weighed. The volunteers were not allowed to scratch during the study.

Substances

The test substances were all diluted in 99% ethanol as follows (weight/volume): 10% aspirin, 1% aspirin, 5% mepyramine and 99% ethanol as a vehicle control. The histamine solutions were prepared from lyophilized crystalline powder (Sigma, St. Louis, Mo., USA) of highest purity, dissolved in sterile physiological saline. The concentration of histamine (0.1 mg/ml) was chosen from the literature (4, 16).

SLS (Sigma), purity > 99%, was diluted in demineralized water to a 1% concentration immediately prior to use.

Statistics

Comparisons of the test areas regarding itch, pain, clinical inflammation scoring, TEWL and skin redness were made using the non-parametric Friedman test with Dunn's Multiple Comparison as post hoc test. Wheal and flare areas were found normally distributed (Kolmogorov-Smirnov test) and were compared by Repeated Measures ANOVA with Bonferroni's Multiple Comparison as post hoc test (the four pretreatments were corrected for three vehicle comparisons). Correlations between itch, pain, wheal, flare, clinical inflammation score, TEWL and redness were assessed using the Spearman test. $P < 0.05$ (two-tailed) was considered significant.

RESULTS

Itch magnitude, duration and total intensity

Itch intensity scores following each of the 10 injections (median values), shown in Fig. 1, demonstrate essentially the same profile, with maximum itch intensity within the first minute, followed by a decline. The itch profile curves were characterized by the parameters: time to maximum itch intensity, duration of itch, the itch magnitude and the *a*rea *u*nder the itch profile *c*urves (AUC). The AUC represents the total itch elicited by histamine; the results are given in the upper third of Fig. 2. None of the three pretreatments was statistically significantly different from their vehicle, neither in normal nor in SLS pretreated skin. After application of aspirin 10% or mepyramine, a significantly higher ($p < 0.05$) itch intensity (median AUC) was seen in SLS inflamed skin compared to normal skin.

Flare and wheal areas

Flare and wheal areas are shown in the lower two-thirds of Fig. 2. Pretreatment with aspirin 10% resulted in significantly smaller flare areas in normal skin ($p < 0.05$) and inflamed skin ($p < 0.01$) compared to the vehicle. Wheal reactions were only smaller in the inflamed skin ($p < 0.01$), but here also application of aspirin 1% led to less pronounced areas compared to the vehicle ($p < 0.05$) (see Fig. 2). Pretreatment with mepyramine led to smaller flares compared to the vehicle ($p < 0.001$ in both skin types). Also the wheals were smaller in normal ($p < 0.01$) and inflamed skin ($p < 0.001$). The

vehicle did not influence the flare and wheal areas compared to not pretreated test sites.

In test sites not pretreated with substance, the flare areas were larger in the normal skin compared to SLS pretreated skin ($p < 0.05$). On the contrary, the wheal sizes were more pronounced in the inflamed skin compared to normal skin ($p < 0.01$).

Pain

Pain was mainly scored to sharpen the volunteer's discrimination between itch and pain, in this way avoiding scoring the overall sensation as itch. Nevertheless, pain records at 1–20 min were available (for median AUC scores from 1–20 min, see Table I). No significant differences in pain intensities were found between the test sites. However, application of ethanol, and especially aspirin 10%, aspirin 1% and mepyramine, led to lower medians, range-values and upper quartiles of pain scores as compared with the test site not pretreated with substance (see Table I).

Clinical scoring, TEWL and redness

All volunteers had some degree of inflammation (as judged clinically) when the 5 chambers were removed after 24 h. The upper four positions on the forearms were not different in their median clinical scores, redness (a* values) or TEWL values. The most distal site was significantly lower in clinical scoring as compared to the upper four positions, while no differences were found for TEWL values and redness (a* values).

Correlation between itch, pain, wheal, flare, clinical inflammation score, TEWL and redness

The median itch and pain scores were not correlated to wheal or flare sizes, clinical inflammation, TEWL or redness. Itch and pain were, like wheal and flare, neither positively correlated nor inversely correlated to each other. On some, but not all, of the sites on the forearm, the delta a* values positively correlated to clinical inflammation score and TEWL values. TEWL values showed very good correlations with clinical scoring for all five positions (Spearman $r = 0.71$ to 0.85 and $p < 0.001$ for all positions).

Temperature and air humidity in the room and in the water bath were measured in the morning and afternoon. There was no difference during the day (Student's *t*-test). For all results, we found no difference between the sexes.

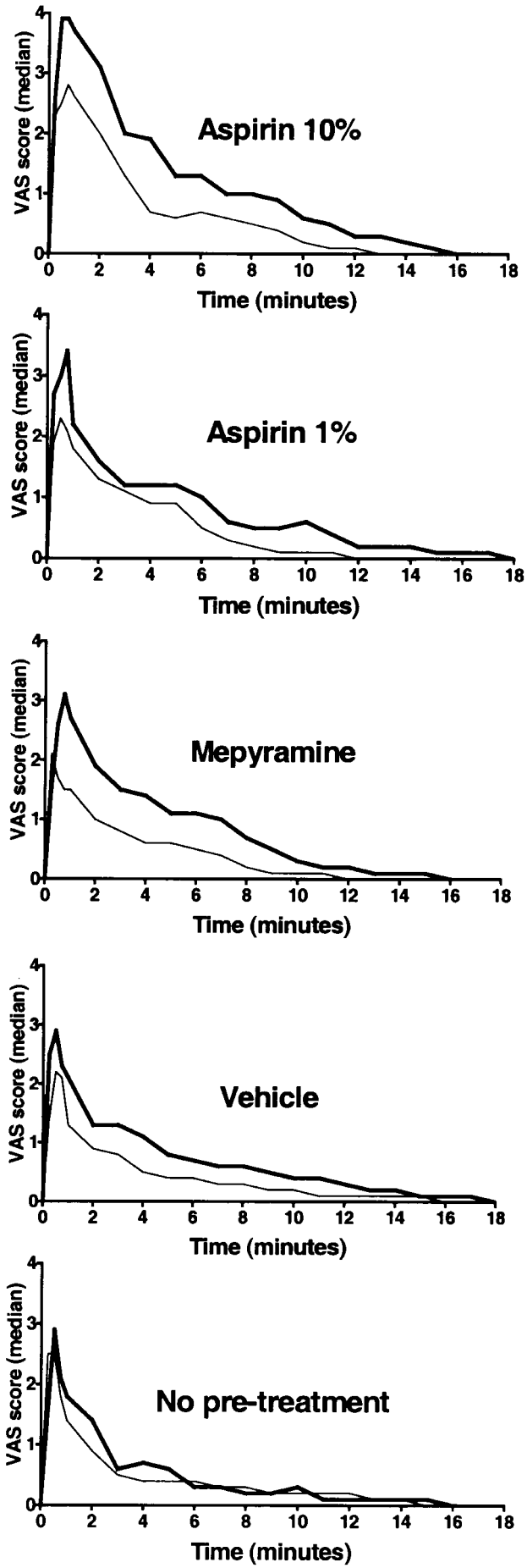

Fig. 1. Itch profile curves of the selection of substances tested in this study. Bold lines represent itch profile curves obtained in SLS-inflamed skin ($n = 24$), and the thin lines the same response in normal skin ($n = 24$).

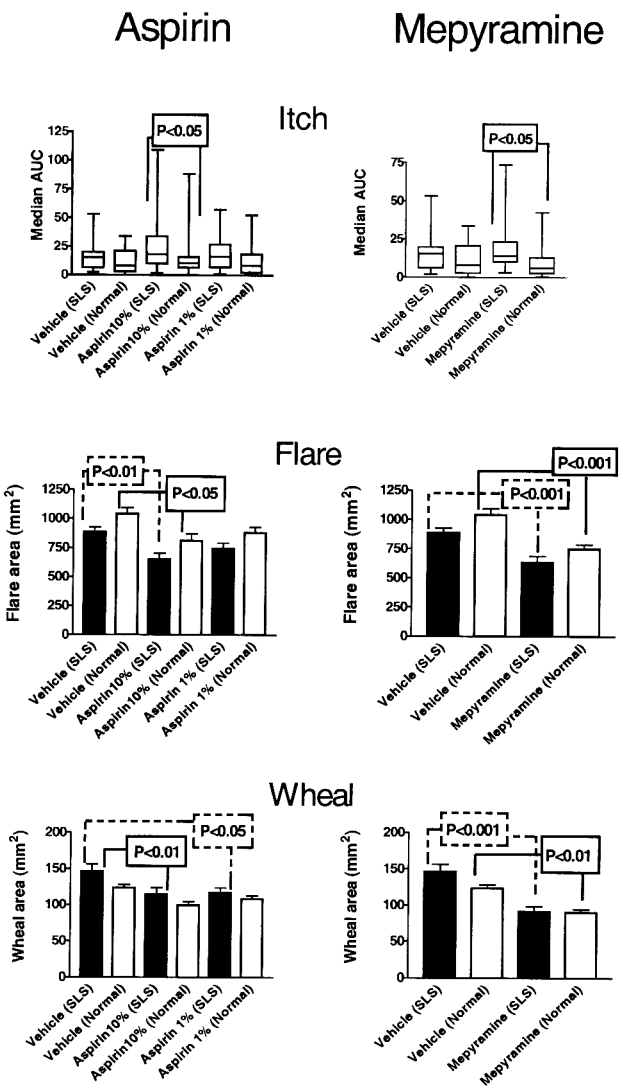

Fig. 2. Itch, flare and wheal response to histamine injections after aspirin and mepyramine application ($n = 24$). *Upper third* is Box & Whiskers plots (medians, quartiles and ranges) of itch scores (AUC). *Medium third* represents flare sizes in mm^2 assessed 5 min after histamine injections. *Lower third* is the wheal area in mm^2 assessed 20 min after histamine injections. Black bars represent injections in SLS-pretreated skin, and white bars injections in normal skin. Mean values and SEM.

Table I. *Pain intensities (medians, ranges and quartiles). From minute 1–20 in the study each test person scored pain intensity on a VAS scale. The cumulated pain scores from min 1–20 represented the total pain score after an injection of histamine. All 25% percentiles were 0.0. N = 24*

	Median (range)	75% Percentile
Normal skin		
Aspirin 10%	0.0 (0.0 to 1.4)	0.0
Aspirin 1%	0.0 (0.0 to 3.3)	0.0
Mepyramine	0.0 (0.0 to 1.8)	0.0
Vehicle	0.0 (0.0 to 2.8)	0.25
No pretreatment	0.0 (0.0 to 6.0)	0.3
SLS pretreated skin		
Aspirin 10%	0.0 (0.0 to 3.5)	
Aspirin 1%	0.0 (0.0 to 1.5)	0.0
Mepyramine	0.0 (0.0 to 2.8)	0.05
Vehicle	0.0 (0.0 to 2.7)	0.25
No pretreatment	0.0 (0.0 to 5.4)	0.9

DISCUSSION

Pretreatment with aspirin 10% and aspirin 1% in both normal and inflamed skin resulted in higher (though not significantly) median itch scores compared to the vehicle. In the study by Yosipovitch et al., itch was exclusively induced in normal skin and, like us, they found that histamine induced itch lasting for 16–17 min in placebo pretreated skin (4). They applied aspirin 3% (w/v) 25 min prior to histamine injections and found that itch duration was reduced to 7–8 min ($p < 0.001$) and that itch magnitude was significantly decreased ($p < 0.04$). In our study, itch duration was 12 min after aspirin 10% and 11 min after aspirin 1% compared to 16.5 min in the vehicle pretreated test areas (see Fig. 1), but both itch magnitude (Fig. 1) and the total itch (AUC) (Fig. 2) were *higher* (though not significantly). Our results therefore both accord with and oppose the results by Yosipovitch et al. (4). Hägermark studied aspirin taken orally, and found that it tended to prolong itch sensation caused by histamine (2).

The Yosipovitch et al. study did not include pain scores. However, we believe that inclusion of pain scores is becoming more and more important in experimental itch studies. In 1997, Schmelz et al. were able to isolate histamine-sensitive C-fibres from human skin using the microneurography technique (17). Like other types of nociceptors, these fibres responded to injection of capsaicin, leading to pain. In a fairly recent paper, Andrew & Craig reported that when histamine was applied to the skin of cats, specific neurones in the spinal cord reacted in an almost similar way to itch experienced by humans (18). These nociceptors had very similar properties to the primary afferents found in humans by Schmelz et al. It therefore seems likely that pain and itch are processed by two anatomically different systems. However, by abolishing pain with local anaesthetics, histamine-induced itch was enhanced and prolonged (19). Conversely, increased pain by capsaicin injection reduced histamine-induced itch (20).

As indicated in Table I, application of aspirin 10% and aspirin 1% led to smaller (though not significantly) 75% percentiles and range pain scores compared to vehicle. The data can therefore be interpreted as including a possible reduction of injection pain by aspirin, which could cause enhanced itch ratings. On the other hand, mepyramine too exhibited lower pain scores, and mepyramine by itself would hardly reduce injection pain. The activity of histamine-sensitive primary afferent "itch fibers" was reduced by the application of aspirin, as can be seen by the smaller axon reflex flare. Histamine type-1 receptors (H_1 receptors) are coupled to the intracellular

phospholipase C (PLC) pathway, while H_2 receptors primarily are coupled to the adenylate cyclase pathway (21). Aspirin has been shown to inhibit PLC (22), so theoretically both wheal and the neuro-mediated itch and flare would be attenuated by aspirin application. Itch was *larger* after topical aspirin, but is also modified by central processing and local pain stimuli.

Mepyramine was included as a presumed positive reference. The lowest of all itch scores was seen in mepyramine-pretreated normal skin, but the result was not significant. In two studies by Weisshaar et al., topical antihistamines reduced histamine-induced itch in one study (13), but not in the other (14). We do not know why mepyramine did not suppress itch in our study. Antihistamines are competitive antagonists to histamine on the H_1 receptor, so the histamine concentration may have been too high to suppress. On the other hand, a concentration of 100 mg/ml has been used earlier (4, 12, 16, 23, 24), and was also injected by Yosipovitch et al. in their study (4).

When aspirin 10% was applied to inflamed test sites, unexpectedly *more* itch ($p < 0.05$) was induced by histamine compared to normal skin pretreated with aspirin 10%. The concentration of prostaglandins is increased in acute skin responses to irritants (25) and in inflammatory dermatoses (26). Since prostaglandins lower the itch threshold (7, 8, 10) and aspirin blocks the formation of prostaglandins, we actually anticipated *lower* itch scores in inflamed test sites pretreated with aspirin compared to non-inflamed sites. Perhaps aspirin as an acid, when applied directly to eczematous skin, is able to influence the sensation coming from the inflamed SLS pretreated skin. Other salicylic compounds may have produced a different result, and in another study by our group, two topically applied salicylic compounds were able to suppress serotonin-induced scratching in rats, while salicylic acid itself did not (27).

Both wheal and flare reactions were influenced by topical aspirin. After pretreatment with aspirin 10%, flares were smaller in normal ($p < 0.05$) and inflamed skin ($p < 0.01$). Wheal was not influenced in normal skin, but in inflamed skin the edema was smaller after pretreatment with aspirin 10% ($p < 0.01$) and aspirin 1% ($p < 0.05$). In earlier studies, topical aspirin also reduced capsaicin-evoked flare in humans (28) and protein extravasation in rats (29), while orally taken aspirin increased histamine-induced flare (2) and wheal (30). These opposite results from systemic and topical aspirin may be due to a true difference. Most topical salicylic compounds are hydrolyzed to salicylic acid in the epidermis (31), but ingested aspirin may enter the blood as acetylsalicylic acid and be present in the dermis not entirely metabolized to salicylic acid (32).

The reduction in wheal and flare areas was more pronounced in inflamed skin than in normal skin, which was probably due to a better skin penetration of aspirin, since in SLS-inflamed skin the penetration of salicylic acid is highly increased compared to that in normal skin (33). Moreover, aspirin can reduce vasodilation under inflammatory conditions. However, given an enhanced endothelia permeability by histamine, vasodilation will indirectly increase protein extravasation (34, 35) and thereby aspirin could indirectly decrease wheal size in inflamed skin. Finally, prostaglandins potentiate flares (1, 10) and wheals (34). Aspirin may therefore block the effect of especially short-lived prostaglandins such as PGH_2 (10), resulting in a larger wheal and flare reduction in inflamed skin compared to normal skin.

We have earlier reported a larger wheal reaction to histamine in SLS inflamed skin using this model (12). Flare has not been studied previously, and opposite to wheal flare was smaller ($p < 0.05$) in inflamed (not pretreated) skin. Patients with atopic dermatitis also produce smaller flares compared to non-atopic controls (36), and it appears that active inflammation in the skin *per se* may be responsible for the smaller flare area (37, 38).

When using the present itch model it is important to assess the degree of skin inflammation. Besides clinical judgement, TEWL can estimate the degree of irritant dermatitis (39), and seems superior to measurements of skin redness.

In conclusion, we could not demonstrate an antipruritic effect of topical aspirin on histamine-induced itch, despite a significant skin penetration as indicated by the influence of aspirin on wheal and flare reactions.

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