

# Separate Effects of Topical Indomethacin on the Itch Response and on the Flare Reaction Induced by Histamine in Human Skin

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The effects of topical indomethacin on histamine responses and histamine release were studied in 15 healthy volunteers. Three hours before testing, the indomethacin solution was applied under occlusion on one arm and the corresponding vehicle on the other. Solutions of histamine and the histamine releasing compound 48/80 were injected intradermally in both arms. Indomethacin treatment inhibited the flare reactions induced by histamine and compound 48/80 to about 50%, whereas no influence was seen on the itch responses. Our results indicate that indomethacin has no effect on the release of histamine, but it selectively suppresses the histamine-induced flare reaction leaving the itch duration unaffected. *Key words: Histamine release; Compound 48/80.* (Received January 8, 1985.)

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In a previous investigation (1) we concluded that topical glucocorticoid treatment could suppress histamine release in human skin. The mechanism for this inhibition was unexplained. However, the possibility of interference in the arachidonic acid metabolism was considered, since arachidonic acid formation is known to be suppressed by glucocorticoids (2), and products of the arachidonic acid cascade might be essential for the histamine release process (3, 4, 5). Arachidonic acid is a precursor both to cyclo-oxygenase products such as prostaglandins and thromboxanes and to lipoxygenase products such as leukotrienes and HETE's.

As a first step in the evaluation of the role of arachidonic acid products in cutaneous histamine reactions, we studied the effects of the cyclo-oxygenase inhibitor indomethacin on histamine responses in human skin. Although indomethacin was not found to inhibit histamine release, we made the interesting observation that it selectively decreased the flare reaction induced by histamine without affecting the itch response. Such a selective influence on the histamine flare reaction is not a rule, but a similar pattern has previously been observed after treatment with the local anaesthetic lidocain (unpublished, Hägermark).

## MATERIALS AND METHODS

Fifteen non-atopic, drug-free volunteers (age 18-57 years) took part in this investigation. Clearly outlined areas, 14x5 cm on the lateral aspect of the upper arms, were used for the experiment. We applied 0.3 ml of indomethacin solution (2.5% w/v in a vehicle of ethanol: propylene glycol: dimethyl

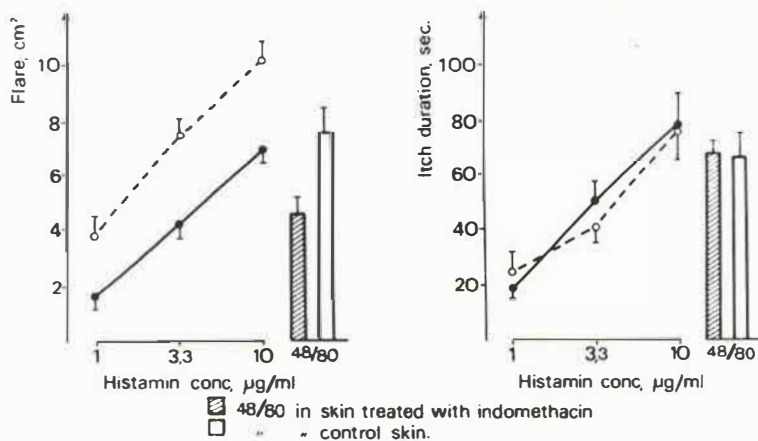


Fig. 1. Dose-response curves for flare and itch reactions induced by histamine in skin treated with indomethacin (●—●) and in control skin (○---○). The bars show responses after injection of compound 48/80 (3.3 µg/ml) in skin treated with indomethacin and in control skin. (Means ± SE;  $n=14$ .)

acetamid 19:19:2 by vol) on one arm and the same amount of the vehicle on the other. An occlusive plastic film was wrapped around the arms and taken away after 3 hours. Solutions of histamine (1, 3.3 and 10 µg/ml) and of compound 48/80 (3.3 µg/ml) were used for testing. Small volumes, 0.01 ml, of the solutions were injected intradermally within the pretreated areas in a double-blind fashion. All injections were given by the same person, using a special adaptor with the syringe in order to obtain accurate volumes (6). The duration of the itch response was recorded. The area of the flare reaction was outlined 5 min after injection, traced onto a plastic film, and measured with a planimeter (model 317, Gebrüder Haff GmbH, Pfronten, West Germany). When the histamine reaction had disappeared approximately 1 hour later, an ointment with 5% tetrahydrofurfurylester of nicotinic acid (Trafuril®, CIBA-Geigy AG, Basel, Switzerland) was applied to the same areas on both arms. The reaction was observed for about half an hour and the intensity of the erythema was noted.

The results were statistically analyzed with the Dixon and Massey sign test (7).

## RESULTS

The erythema following the application of nicotinic acid ester (Trafuril®) was markedly reduced on the arm treated with indomethacin in 14 of 15 subjects, indicating that the indomethacin solution had been absorbed into the skin. One subject had an intense Trafuril® reaction and he was therefore excluded from the study (the histamine-induced flare reactions were unaffected by treatment with indomethacin in this subject as well).

In all of the remaining 14 subjects, indomethacin pretreatment suppressed the flare responses induced by both histamine and the histamine releasing agent compound 48/80 by 35–55%. The itch responses were, however, unaffected by the same treatment (Fig. 1).

## DISCUSSION

Antiinflammatory drugs, such as aspirin and indomethacin which block cyclo-oxygenase activity, are known to inhibit Trafuril®-induced erythema (8). In this investigation, treatment with indomethacin markedly suppressed the Trafuril® reaction. We therefore concluded that the indomethacin solution was effectively absorbed into the skin.

In agreement with other investigators, who have found that indomethacin cannot suppress histamine release in vitro (9, 10), our results indicate that indomethacin did not inhibit 48/80-induced histamine release in human skin. The flare reactions induced by both compound 48/80 and exogenously injected histamine were equally suppressed, and the itch responses were not affected at all. This is in contrast to what we found after corticosteroid treatment which inhibited the reactions induced by compound 48/80 to a much greater

degree, indicating a suppression of histamine release (1). These findings are in accordance with recent theories suggesting that cyclo-oxygenase products are not involved in the histamine release process, whereas lipoxygenase metabolites may play an essential role in basophil activation and secretion (10, 11).

The reduction in flare size may be due to the suppression of prostaglandin formation. However, intradermally injected prostaglandins are known to enhance both the itch and the flare induced by histamine (12). In this study only the flare responses were suppressed, while the itch duration was unaffected. Thus, the separate effects on the itch and flare responses after indomethacin might require another explanation than the simple suppression of prostaglandin formation.

The mechanism by which the flare reaction arises is not completely understood. However, recent experiments support the theory of a neurally mediated model of axon reflex erythema spread (13). The mediator for this reaction is not known, but considerable evidence suggests a role for the neuropeptide substance P (14). Indomethacin-induced inhibition of a presumably substance P-mediated activity is a purely speculative thought, but it might explain the dissociation between itch and flare responses in our study.

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