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Topical Indomethacin Aggravates the Weal and Flare Response in Chronic Dermographic Urticaria: Evidence for a New Class of Histamine Receptors

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The effect of topical indomethacin on the weal and flare response was measured in 9 patients with chronic dermographic urticaria. An augmentation of dermographic wealing by topical indomethacin was shown with lowering of the weal threshold from 22.3 ± 4.7 g/mm² (mean ± SEM, $n = 9$) to 16.4 ± 3.8 ($p < 0.005$), but without a change in the shape of the force/response curve. Flare was increased by indomethacin particularly in patients with a greater lowering of the weal threshold. The augmentation of weal and flare by indomethacin in individual patients was not related to the degree of inhibition of UVB erythema in individual patients. These findings indicate that in chronic dermographic urticaria there is an abnormality involving eicosanoid production by a non-cyclo-oxygenase pathway. It is suggested that this acts by augmenting the effect of histamine on a new class of histamine receptor, the definition and antagonism of which should lead to better control of urticarial disease.

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Wealing in chronic idiopathic urticaria and chronic dermographic urticaria is only partially inhibited by H_1-receptor antagonists in doses sufficient to inhibit histamine wealing virtually completely (1, 2). This suggests that mediators other than histamine acting on the H_1-receptor are also important in the wealing process of the urticaria. The well-known exacerbation of chronic idiopathic urticaria that occurs with aspirin and other cyclo-oxygenase inhibitors suggests involvement of metabolites of arachidonic acid, other than those produced by the cyclo-oxygenase pathway. Since, however, a topical preparation of indomethacin, sufficient to inhibit UVB erythema, was without effect on the weal and flare response to histamine, 48/80 and house dust mite (HDM) antigen in normal subjects (3), it was concluded that the worsening of chronic urticaria by cyclooxygenase inhibitors was related to the urticarial disease process. To test this we have studied the effect of topical indomethacin on the wealing and flare response of chronic dermographic urticaria.

MATERIALS AND METHODS

Nine patients (3 male, 6 female, age range 21–69, mean 42 years) with chronic dermographic urticaria for at least 2 months were studied. None had ever taken astemizole and none had taken other antihistamines for at least 3 days before the study. All patients gave informed consent to the study, which had been approved by the Newcastle Health Authority ethical committee.

To confirm the bioactivity of the indomethacin gel, a small area of the paraspinal skin on both sides was irradiated with a test dose of UVB radiation using a 500-W medium-pressure mercury arc lamp. The radiation was filtered with Schott WG305 (3 mm thick) and UG5 (1 mm thick) colour glass filters and focused into a liquid-filled light guide with an applicator at the distal end to produce a uniform beam of radiation 1 cm in diameter. The radiation given (40–65 mJ/cm²) was estimated to be 2–3x the minimal erythema dose. Immediately after irradiation indomethacin 1% gel (Amuno Gel, MSD Sharp & Dohme, München, Germany) was applied to a 25 x 6 cm rectangle of paraspinal skin including the test site and gel base to the other side. The areas were occluded with paraffin film for 18 h, after which the gel was removed, and 30 min later the erythema at the UVB test sites was measured with a reflectance instrument which obtains an erythema index related to blood content of the superficial dermis (4). The increase in erythema over an unirradiated control site was measured 4–6 times at each site.

The wealing response to a frictional force was measured using a spring loaded stylus traversed 3 times across a metal guide plate with a 55 mm slot. Using 10 different spring pressures, established by calibration using a spring balance, the weal diameter (mm) induced after 10 min was measured in triplicate along the linear weal. A frictional force/weal response curve over the spring pressure range of 17.5–95.5 g/mm² was obtained by non-linear regression (algorithm of Marquart). The relationship for regression was: $w(p) = M(1-\exp(-k(p-T)))$; $w(p)$ = weal diameter at spring pressure p, M = maximum weal, k = exponential constant, p = spring pressure, T = weal threshold (spring pressure) (Sharpe & Shuster, to be published). Flare was noted subjectively in all patients and measured in 4 patients using a scanning laser-Doppler meter (5).

RESULTS

The increase in erythema for UVB irradiated skin sites was 0.169 ± 0.024 (mean ± SEM, $n = 7$) after the gel base and 0.094 ± 0.018 after the indomethacin gel. This significant inhibition of UVB erythema by indomethacin ($p < 0.002$, paired t-test) confirmed the penetration and bioactivity of the indomethacin gel.

The frictional force/weal response curves in a single patient before and after indomethacin are shown in Fig. 1 and are typical of the findings in all the patients. Both curves are similar, but the threshold for response is lower after indomethacin and at all pressures the mean weal response is greater with the indomethacin than with the gel base. The wealing response above the threshold stylus pressure is a good approximation to a linear relationship initially, but not as the stylus pressure increases and the response approaches a plateau or maximum wealing. However, all the data points may be fitted to an exponential curve by non-linear regression. The mean stylus pressure/weal response curve of all the data (Fig. 2) also shows the augmenting effect of indomethacin, but the shape of the curve is different from that seen in an individual patient because of the threshold differences between patients and the effect of meaning non-linear curves. Non-linear regression curves were therefore obtained for each patient and the calculated values of the weal threshold and maximum weal compared between the control and indomethacin treatments.

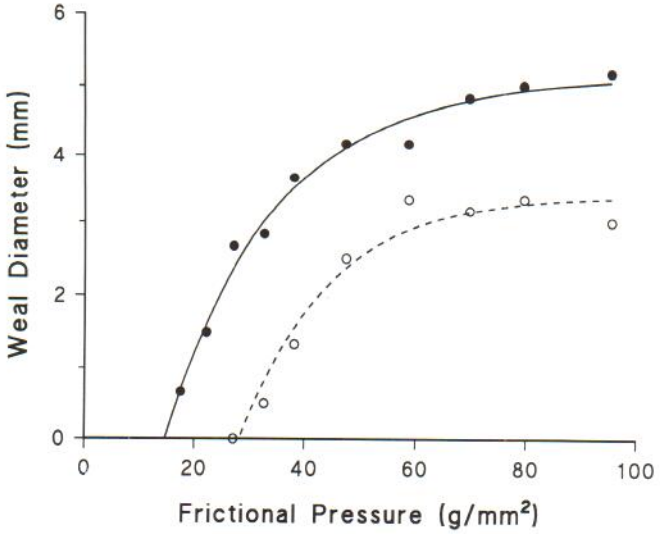

Fig. 1. Frictional pressure/weal response curve for a single patient with gel base (○----○) and indomethacin gel (●——●). The regression line is w (p) = M (l-exp (-k (p-T))); w (p) = weal diameter at pressure p, M = maximum weal, k = exponential constant, p = pressure, T = weal threshold (pressure).

The wealing threshold was 22.3 ± 4.7 g/mm² (mean ± SEM, $n = 9$) after the gel base and was significantly reduced to 16.4 ± 3.8 by the indomethacin gel ($p < 0.005$ paired t-test) (Fig. 3). Although the maximum weal diameter at the plateau of the curve was greater after indomethacin in some patients, the mean values were 5.23 ± 0.49 mm for the base and 5.34 ± 0.54 for indomethacin, and this increase is not significant (Fig. 4). The changes in exponential rate constant of the spring pressure/weal response curves were similar to the maximal wealing, but overall was not different between the base, 0.046 ± 0.005, and the indomethacin gel, 0.052 ± 0.009. Thus indomethacin shifts the pressure/weal response curve upwards and to the left (lower wealing threshold) without changing its shape.

A greater degree of erythema around weals was observed on the indomethacin-treated side in 6 of the 9 patients. This effect

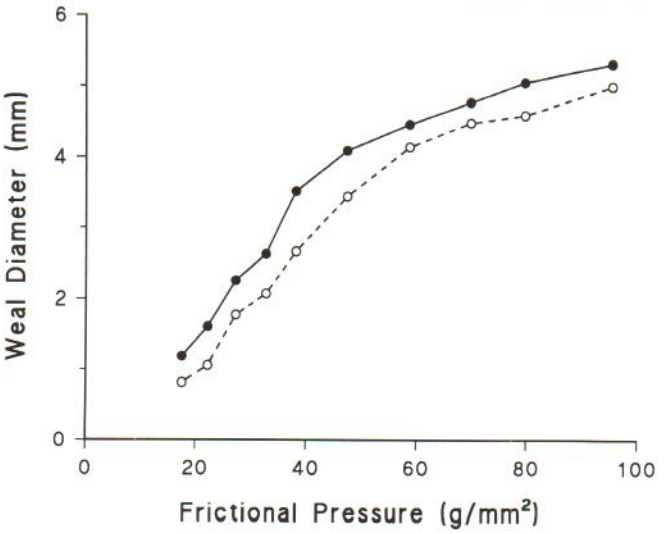

Fig. 2. Mean frictional pressure/weal response curve ($n = 9$) for gel base (○----○) and indomethacin gel (●——●).

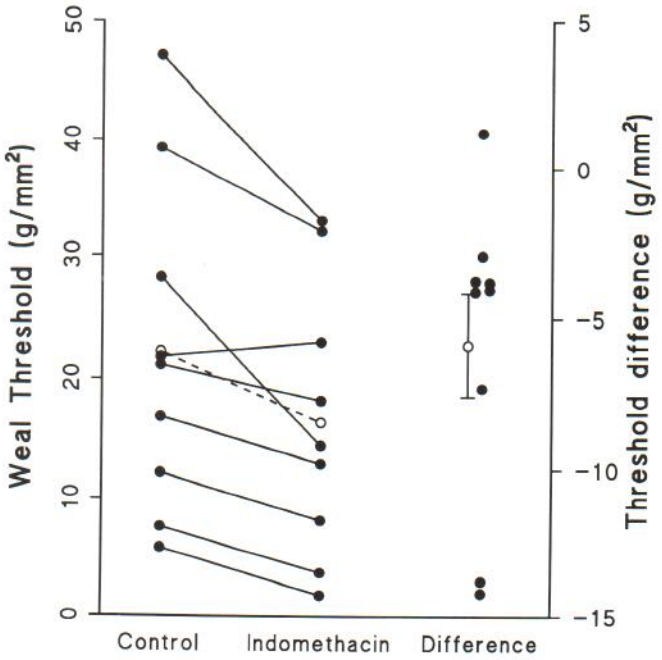

Fig. 3. Weal threshold pressure (g/mm²) for gel base and indomethacin gel. $n = 9$, mean shown by dashed line; difference shown on the right, with mean difference ± SEM.

was most marked in those patients with the greatest lowering in the wealing threshold by indomethacin, but was not related to the degree of inhibition of UVB erythema by indomethacin. Likewise there was no relationship between the change in wealing and degree of inhibition of UVB erythema.

DISCUSSION

We have demonstrated an augmentation of flare and der-

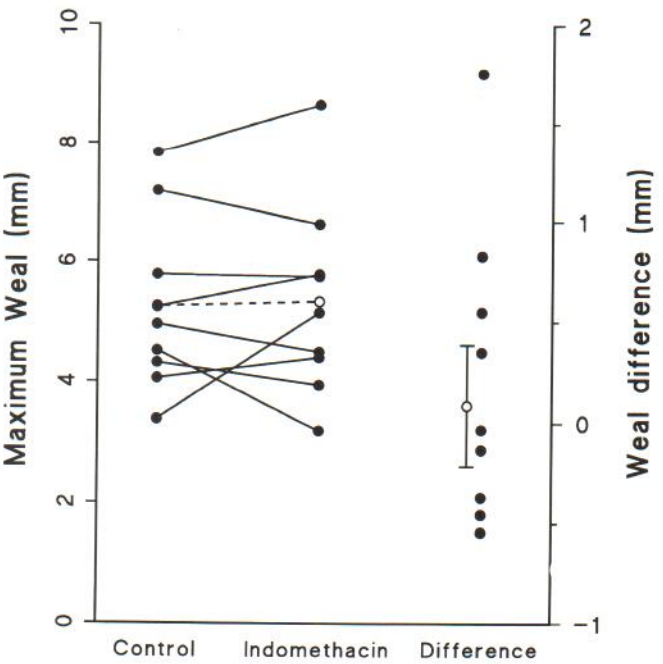

Fig. 4. Maximum weal (mm) for gel base and indomethacin gel. $n = 9$, mean shown by dashed line; difference shown on the right, with mean difference ± SEM.

mographic wealing by topical indomethacin with lowering of weal threshold, but without a change in the shape of the frictional force/response curve.

The method we have used for measuring dermographism is well established and reproducible (6), except that the use of an exponential regression analysis has improved on previous studies because it provides a better description of the force/response relationship and therefore allows analysis of all points on curve. Likewise the use of indomethacin gel topically to inhibit cyclo-oxygenase activity has been well established, and we confirmed bioefficacy in our patients by measuring inhibition of the UVB erythema response (7). Thus despite the small numbers of patients studied the responses were reproducible and large enough to demonstrate a clear augmentation of dermographic urticaria by indomethacin.

The augmentation of wealing was seen both as a decrease in the threshold force and as an increased weal response to frictional force throughout the force-response curve. Although we did not measure flare in all patients, it was clearly affected in the same way as wealing. Clinically, change in the weal threshold is more important than the position of the dermographic force/response curve beyond it, because it relates better to the onset of itch and therefore the initiation of scratching and the provocation of further itch and scratch-provoked wealing (8). In some of the patients the plateau of the dose-response was higher after indomethacin, and with it the slope of the curve. Whether this was a chance or real finding requires confirmation, since a non-parallel shift in the dose-response curve has considerable mechanistic significance. Nevertheless our findings of augmentation of weal and flare by indomethacin in patients with urticarial disease contrast with its lack of effect on wealing from histamine, 48/80 and house dust-mite in normal subjects without urticarial disease and confirm that the response to indomethacin is related to the urticarial disease process (3).

Definition of the defect revealed by indomethacin is of considerable theoretical and practical importance, since urticarial disorders are only partially controlled by drugs producing total H_1 receptor blockade (1, 8) and H_2 receptor antagonists have little additional effect (9, 10). The augmentation of weal and flare by indomethacin in patients with urticarial disease is presumably caused by the change in production of eicosanoids resulting from cyclo-oxygenase inhibition and substrate deviation. The question is whether this aberrant production of eicosanoids augments the response to histamine or has an independent vasoactive action. The weal and flare response has a greater resemblance to the reaction to histamine than to the eicosanoids. Likewise the finding of an enhanced response to histamine in patients with chronic idiopathic urticaria (11) and a further augmentation of this response in those in whom the condition is made worse by aspirin (12) suggests that augmentation of the reaction is caused by histamine itself. However, our preliminary studies suggest that the augmentation of dermographic wealing by indomethacin cannot be inhibited by virtually total H_1 receptor antagonism by astemizole. Thus if these findings are confirmed, they indicate that the addition vasoactive component in chronic idiopathic and dermographic urticaria, and which accounts for at least 35% of the weal and flare of condition (8), is due to the effect of histamine itself acting on a receptor other than the H_1 receptor. From our own and other studies (9, 10) it is apparent that the H_2 receptor has minimal involvement, and we therefore propose that this novel action of histamine must occur on an entirely new class of histamine receptors. Definition of this receptor and the synthesis of its antagonists would therefore provide a new approach to the treatment of urticarial disease. Furthermore there are other instances where this putative histamine receptor may be involved pathologically; for example although indomethacin inhibits UVB-induced erythema in normal subjects, the drug exacerbates the UV response in diseases such as actinic prurigo (13).

We conclude that the exacerbation of dermographic wealing and flare by indomethacin indicates an abnormality involving eicosanoid production by a non-cyclo-oxygenase pathway which may augment the response to histamine other than by the H_1 receptor. This probably explains why chronic idiopathic urticaria and dermographic urticaria are only partially suppressed despite total H_1 receptor inhibition and why the urticarial disorders are made worse by non-steroidal anti-inflammatory drugs.

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