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# INDOMETHACIN IN URTICARIA AND HISTAMINE INDUCED WEALING

## A double-blind evalution

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Indomethacin, a new nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties (11, 12) has been found effective in a number of rheumatic diseases (2, 7, 11, 13). Lately its effect has been studied in a number of inflammatory dermatological disorders (4, 6, 9, 15). However, indomethacin, has not yet found a definite place within dermatology. The following is a report on an investigation designed to evaluate the efficacy of indomethacin in urticaria. Its effect on histamine-induced wealing was also investigated.

### Methods and Materials

The study included 24 patients aged 13 to 74 years, suffering from urticaria, mainly of the chronic or recurrent type. All had undergone a thorough, but unsuccessful medical study to find the cause of their disease. Several patients had noticed exacerbations of their hives during periods of mental stress. A control group of 10 patients suffering from recurrent attacks of herpes simplex was included in the study. The control group patients were 16 to 50 years of age. Six of the urticaria patients and 3 of the herpes patients participated in the study on the effect of indomethacin on histamine induced wealing. This part of the study also included five patients with herpes zoster and two patients with erythema multiforme, who for other reasons, received either indomethacin or placebo in a double-blind study (15). Patients with peptic ulcer, gastritis, ulcerative colitis and similar gastrointestinal disorders were not included in our investigation.

All patients received either indomethacin[1] or placebo.[1] The drug and placebo were identical in appearance, and at no time during the experiment was the physician or the patient aware of which medication was taken. The dosage was one capsule three times daily. Each indomethacin capsule contained 25 mg of the active drug. During the clinical trial the patients were examined initially and on a weekly basis until the study was terminated four weeks later. Two of the control patients, however, were only treated for two weeks. Each week, scores were given for severity of disease and for severity of itch or pain. The grading of the scores was 0=none, 1=mild, 2=moderate and 3=severe. On completion of the trial the patients and the physician evaluated the response subjectively and objectively (change in itch and pain, disappearance or decrease in number of lesions and length of free period). The overall appraisal of the effectiveness of therapy was based partly on the patients judgment,

[1] Kindly supplied by Merck, Sharpe & Dohme.

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partly on the observations of the investigators. The effect of therapy was graded as 1=poor, 2=fair, 3=good and 4=excellent. It was also noted if the disease was still present on termination of the study.

No patients with lesions of the forearms on the day of testing were included in the study of histamine-induced wealing. In this part of the investigation, the intradermal tests were undertaken on the flexor surfaces of the forearms with 0.1 ml doses of 100 µg histamine in aqueous solution. The tests were carried out before and after four weeks of treatment with either indomethacin or placebo. After 15 minutes the resultant weals were outlined in ink and traced on transparent paper. Later the areas of the weals were measured planimetrically.

A weekly leukocyte count was done on all patients.

Table 1. *Results of indomethacin treatment of patients with urticaria*

| Case no. | Age | Sex | Duration of disease before therapy | Response to therapy [1] | Disease present after therapy | Side effects [2] |
|---|---|---|---|---|---|---|
| 1 | 44 | F | 3 months | 3 | No | D, H, L |
| 2 | 54 | F | 3 1/2 years | 2 | Yes | None |
| 3 | 24 | F | 4 months | 1 | Yes | D |
| 4 | 47 | M | 8 years | 3 | Yes | D, N, L |
| 5 | 36 | M | 1 week | 1 | Yes | None |
| 6 | 43 | F | 4 years | 2 | Yes | L, O |
| 7 | 24 | F | 2 years | 2 | Yes | None |
| 8 | 35 | F | 10 years | 1 | Yes | H |
| 9 | 24 | F | 1 month | 3 | Yes | D |
| 10 | 19 | F | 3 months | 3 | No | D |
| 11 | 20 | F | 3 days | 4 | No | N |
| 12 | 32 | F | 20 years | 1 | Yes | D, H, N |
| 13 | 59 | M | 1 day | 4 | No | D |
| 14 | 45 | M | 1 month | 4 | No | D, L |

[1] 1: poor, 2: fair, 3: good, 4: excellent.

[2] D: Dyspepsia or other gastrointestinal disturbance, H: Headache, N: Other neurological complaints, L: Drop in leucocyte count >2000, O: Other side-effects (in case no. 6 leg edema).

Table 2. *Results of placebo in patients with urticaria*

| Case no. | Age | Sex | Duration of disease before therapy | Responce to therapy [1] | Disease present after therapy | Side effects [2] |
|---|---|---|---|---|---|---|
| 15 | 71 | F | 4 years | 2 | Yes | D, N, L |
| 16 | 60 | F | 1 day | 2 | Yes | H |
| 17 | 40 | F | 10 years | 3 | No | None |
| 18 | 13 | M | 6 months | 2 | Yes | L |
| 19 | 44 | M | 9 months | 3 | No | None |
| 20 | 48 | M | 1 week | 2 | Yes | D |
| 21 | 15 | F | 1 week | 1 | Yes | H |
| 22 | 31 | M | 2 years | 2 | Yes | N |
| 23 | 74 | M | 12 years | 1 | Yes | None |
| 24 | 37 | F | 2 months | 1 [3] | Yes | D |

[1] 1: poor, 2: fair, 3: good, 4: excellent.

[2] D: Dyspepsia or other gastrointestinal disturbance, H: Headache, N: Other neurological complaints, L: Drop in leucocyte count >2000.

[3] Not included in general evaluation of therapy due to discontinuation of therapy after one week on account of severe abdominal pain.

Table 3. *Results of indomethacin or placebo in patients with herpes simplex*

| Case no. | Age | Sex | Drug[1] | Response to therapy | Side effects[2] |
|---|---|---|---|---|---|
| 1 | 50 | M | I | 2 | None |
| 2 | 32 | M | I | 1 | D, L |
| 3 | 23 | M | I | 1 | H, L |
| 4 | 16 | M | I | 1 | L |
| 5 | 16 | F | P | 1 | None |
| 6 | 24 | M | P | 2 | None |
| 7 | 24 | F | P | 2 | None |
| 8 | 31 | F | P[3] | 3 | None |
| 9 | 29 | M | P[3] | 2 | None |
| 10 | 29 | M | P | 2 | None |

[1] 1: poor, 2: fair, 3: good, 4: excellent.
[2] D: Dyspepsia or other gastrointestinal disturbances, H: Headache, L: Drop in leucocyte count >2000.
[3] Two weeks treatment only.

## Results

Table 1 shows the results as well as the side-effects of indomethacin in 14 patients with urticaria. Table 2 shows the results and side-effects in 10 other urticaria patients treated with placebo (one patient discontinued treatment due to severe abdominal pains). Table 3 shows the results of therapy and side-effects after indomethacin or placebo in 10 patients with recurrent herpes.

The responses to indomethacin and placebo appear from Fig. 1, Fig. 2 and Table 4. The results illustrated in the figures are based on the weekly scorings in patients with urticaria, while the results in Table 4 are based on the physicians' overall appraisal of therapy. Fig. 1 shows the response of itch to indomethacin or placebo. Pain was no common symptom in the urticaria patients. Fig. 2 shows grading of severity of disease during therapy. These evaluations show no significant differences between indomethacin and placebo. Table 4 also shows a comparison of responses to therapy and of side-effects in the two groups of patients. While a comparison of the effect of therapy in the two groups seems to bring out no difference—specially as the indomethacin treated group of herpes patients is so small—the comparison

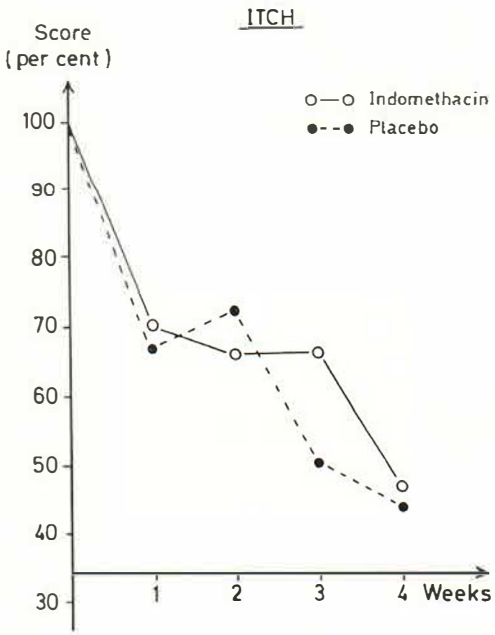


Fig. 1. Comparison of weekly scores for itch in urticaria patients treated with indomethacin or placebo. Scores are expressed in per cent of score prior to therapy.

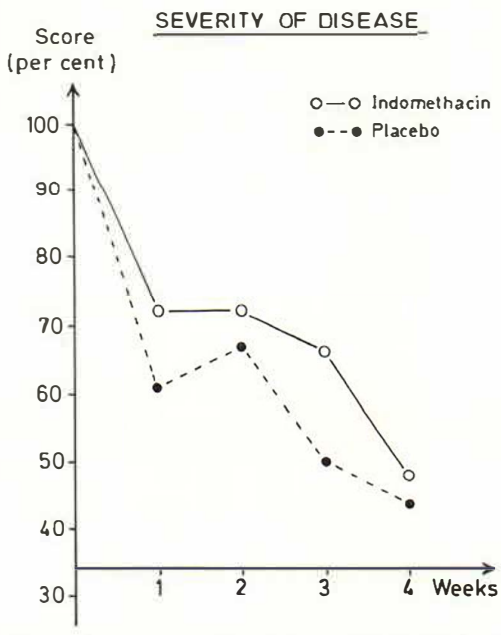


Fig. 2. Comparison of weekly scores for severity of disease in urticaria patients treated with indomethacin or placebo. Scores are expressed in per cent of score prior to therapy.

Table 4. *Comparison of responses to indomethacin and to placebo in urticaria and recurrent herpes simplex (control group)*

| | Urticaria | | Herpes simplex | |
|---|---|---|---|---|
| | Mean effect ± S.E. (score) | Subjective side effects (per cent) | Mean effect ± S.E. (score) | Subjective side effects (per cent) |
| Indomethacin | 2.43 ± 0.36 | 79 | 1.25 ± 0.25 | 50 |
| Placebo | 2.00 ± 0.24 | 60 | 2.00 ± 0.26 | 0 |

Table 5. *Size of weals induced by 100 µg histamine, before and after 4 weeks' treatment with indomethacin, 25 mg three times daily*

| Case no. | Age | Sex | Diagnosis[1]) | Size of weal in mm² | |
|---|---|---|---|---|---|
| | | | | Before | After |
| 1 | 14 | M | H.Z. | 1021 | 785 |
| 2 | 22 | M | H.S. | 788 | 964 |
| 3 | 16 | M | E.M. | 2442 | 1667 |
| 4 | 70 | M | U. | 1236 | 1714 |
| 5 | 47 | M | H.S. | 1416 | 1014 |
| 6 | 39 | M | E.M. | 924 | 1125 |
| 7 | 32 | F | H.Z. | 1021 | 1023 |
| 8 | 35 | M | U. | 399 | 729 |
| Mean ± S.E. | | | | 1156 ± 213 | 1128 ± 131 |

[1] H.S.: Herpes simplex, H.Z.: Herpes zoster, E. M.: Erythema multiforme, U: Urticaria.

Table 6. *Size of weals induced by 100 µg histamine, before and after 4 weeks' treatment with placebo capsules 3 times daily*

| Case no | Age | Sex | Diagnosis[1]) | Size of weal in mm² | |
|---|---|---|---|---|---|
| | | | | Before | After |
| 9 | 73 | M | U. | 1909 | 2072 |
| 10 | 20 | M | H.Z. | 1267 | 952 |
| 11 | 65 | F | H.Z. | 988 | 988 |
| 12 | 29 | M | H.S. | 1521 | 1100 |
| 13 | 71 | F | U. | 789 | 878 |
| 14 | 23 | F | H.Z. | 658 | 764 |
| 15 | 44 | M | U. | 1216 | 1278 |
| 16 | 60 | F | U. | 1717 | 1216 |
| Mean ± S.E. | | | | 1258 ± 152 | 1156 ± 144 |

[1] H.S.: Herpes simplex, H.Z.: Herpes zoster, E. M.: Erythema multiforme, U: Urticaria.

of side-effects seems to give significant data. A marked difference in "placebo side-effects" was found between urticaria patients and patients with recurrent herpes simplex. No placebo treated patients with herpes had side-effects, while six out of ten patients with urticaria complained of side-effects after placebo.

The results of the investigation on histamine induced wealing are summarized in Tables 5 and 6. Treatment with 75 mg indomethacin daily for 4 weeks did not reduce histamine weals significantly. Neither did the control study with placebo show any significant alterations in histamine wealing.

### Comments

Urticaria is a vascular reaction pattern of the skin characterized by transient wealing. According to Lewis & Grant (8) the weals may be the result of liberation of a histamine-like substance. Although the importance of histamine in the pathogenesis of urticaria is still under dispute (1, 5, 10, 14), anti-histamine substances probably acting as competitive inhibitors of histamine (3) are still the most common drugs used in this disorder. Treatment with anti-histamines, however, has its limitations. A pronounced drowsiness follows therapy with even moderate doses, and in severe cases the effect of anti-histamines is not sufficient to keep the patients from wealing. Therefore, new drugs and new methods of therapy have constantly been tested.

The results of the present double-blind study show, that, although a number of patients improved during the study, there was no greater subjective or objective benefit from indomethacin than from placebo. This observation together with the lack of inhibition of histamine wealing is in accordance with the assumption that the anti-inflammatory effect of indomethacin is not This observation together with the lack of anti-pruritic effect of indomethacin, which usually shows analgesic properties (12) should be considered on the background of the different qualities of pain and itch.

The present study allows no conclusions concerning a possible effect of indomethacin on recurrent herpes simplex. The marked difference in side-effects between patients suffering from herpes and patients with urticaria, is probably due to the fact that patients with chronic urticaria are often emotionally unstable and hyper-reactive. This makes any evaluation of therapy within this group of patients extremely difficult. Undoubtedly, a large number of the subjective side-effects noted in this study may not be true drug reactions, even if their characters are similar to reactions reported in previous studies on indomethacin (2, 4, 6, 7, 11, 13). The drops in the leukocyte count should also be considered with caution. In some of the cases they may be side-effects of therapy, while in other instances, they may be changes due to a variation in the activity of the disease. This may especially be true of the patients with herpes simplex.

## SUMMARY

Twenty-four patients with urticaria, mainly of the chronic type, were followed in a double-blind study designed to evaluate the therapeutic effect of indomethacin. Ten patients with recurrent herpes simplex served as a control group. No greater subjective or objective benefit was noted in the indomethacin group as compared to the placebo group.

While 60 per cent of the patients suffering from urticaria had subjective "placebo side-effects", no herpes simplex patients displayed such side-effects. This difference between the two groups is considered characteristic.

The investigation included a double-blind study of the effect of indomethacin on histamine weals in sixteen patients with various skin diseases. Treatment with 75 mg indomethacin daily for four weeks did not reduce significantly histamine wealing. Neither did the control patients show any significant alterations in histamine wealing after four weeks.

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