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THE ANTIPRURIGINOUS EFFECT OF R 516 (GLANIL®) IN SKIN DISEASES

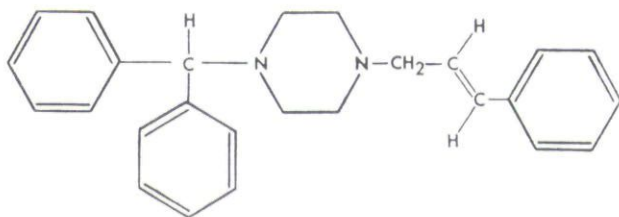
A Double-Blind Investigation

By

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R 516 is a new piperazine derivative, 1-benzhydryl-4-cinnamylpiperazine, which has pronounced anti-histaminic properties.

Structural Formula:



Acute and chronic toxicity in animal tests was found to be extremely low. The anti-histamine effect has been demonstrated by histamine-aerosol tests using guinea pigs. R 516 has a certain inhibiting effect on apomorphine-induced vomiting in dogs. Blood pressure, respiration, and the gastrointestinal tract do not appear to be affected in any particular manner (1). The effects of R 516 are stated to be rapid in onset and persistent; in animal tests, protection against histamine-induced bronchiolar constriction was shown to persist for 24-48 hours following a single dose (1).

The normal daily clinical dose recommended is 15 mg, although this dose may be doubled without any risk of side effects.

R 516 has been tested in different allergic conditions, against pruritus, and for motion sickness. Favourable results have been reported in allergic rhinitis and asthma (2, 3, 4). The incidence of side effects was low. Only 9 of the 80 patients treated experienced side effects: 7 drowsiness of varying degrees, 1 slight headache, 1 dryness of the mouth (3).

With regard to the antipruritic effect of R 516 in cases of itching dermatoses, only one investigation has been published. This report claims good results (4).

We have tested the antipruritic properties of R 516 on patients suffering from skin diseases and pruritus. The tests were carried out by a special double-blind method.

Intensity and duration of Itching.

The patients have recorded the intensity and duration of their itching throughout the entire test period. Intensity has been graded from 0–10. Each day has been divided up into four 6-hour periods and, for each such period the duration of itching was given in hours from 1–6. From the records of intensity values and duration lengths, the intensity of the itch per hour within each 6-hour period—"the itching index"—was calculated according to the formula:

$$\frac{\text{Duration} \times \text{Intensity}}{6}$$

A. Without Therapy.

As we know from experience that itching in many skin diseases regress upon hospitalization it is of the greatest importance to watch for spontaneous improvement during the first days of hospitalization. After this period of observation a more accurate study of the possible antipruritic effect of a drug is possible.

A placebo (placebo I) was given during the first 6 days of hospitalization to 17 patients suffering mainly from eczema which was only treated locally with current soothing preparations. They recorded their itching as described above, after which the mean of the itching index for all 17 patients were plotted on the

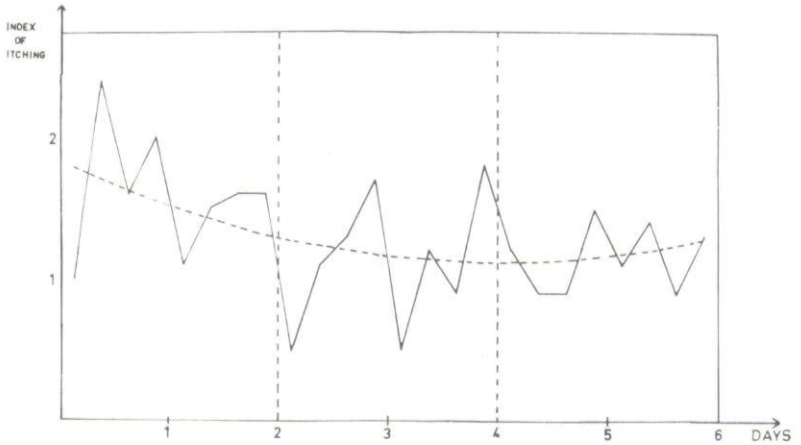


Fig. 1.

Itching index for 17 patients with skin diseases during hospitalization and therapy with placebo and indifferent topical modification.

Y-axis of a co-ordinate system, the time in days being plotted on the X-axis. By joining these mean values, the continuous curve illustrated in Fig. 1 was obtained. The trend in this time series is described by a second degree curve with the equation: $Y = 1.15 - 0.11 X + 0.0007 X^2$ (*origo* between the 12th and 13th 6-hour period), and denoted by the dashed curve in Fig. 1. Thus, the trend gives the average intensity of the itch during the first six days of hospitalization. It can be seen that itching regressed most strongly during the first two days and then remained relatively constant during the 3rd, 4th, 5th and 6th days.

Since in hospitalized patients itching thus normally regresses quickly and spontaneously during the first two days of hospitalization, the double-blind tests were not commenced until the itch had become stabilized at a comparatively steady level, i.e. after these first two days in hospital.

B. With R 516 Therapy.

The material comprised 36 patients, 6 men and 30 women, aged between 17 and 71 years, all suffering from intense itching. Most of the patients had eczematous disorders although other diseases were also noted (Table 1). The patients recorded the intensity and duration of itching as described above, after which the index of itching was calculated.

TABLE 1

Diagnosis of 36 patients with skin diseases treated with R 516.

Diagnosis	No. of patients
Atopic dermatitis	13
Eczema	18
Psoriasis	1
Lichen ruber planus	1
Pruritus	1
Polymorphous light eruption	1
Dermatitis herpetiformis	1
Total.....	36

Most of the patients were given only placebo tablets during their first two days in hospital (placebo I) and the double-blind tests followed immediately. In a few cases, this tests was carried out at a later period when the itching was considered to be relatively stable. In these last patients, too, the test period commenced with two days placebo medication (placebo I). This introductory placebo (placebo I) was known to the investigator and was administered in order to conceal from the patients, as far as possible, the change-over to the comparative experiment.

The four days chosen for the comparative double-blind test were divided into two periods of two days (periods 2 and 3). During period 2, half the number of patients, chosen at random, were given R 516 and the remainder were given Placebo II. During period 3, the latter group was transferred to the drug and the former group to placebo II.¹ This procedure eliminated the effect on the test results of any spontaneous regression of the itching symptom, even if the itch, as previously shown, is normally noticeably steady during periods 2 and 3. The test was carried out using the double-blind method, i.e. neither the investigator nor the patient know which period

¹ The tablets were kindly supplied by AB Mekos, Hälsingborg. R 516 is sold in Sweden under the name of Glanil®.

R 516 or placebo II was being administered. The dosage was 1×3 tablet daily between meals the daily dose of R 516 thus being 15 mg.

Each patient compared the effect of R 516 and of placebo II, for the corresponding 6-hour periods, i.e. 8 such comparative periods per patient. During those periods in which R 516 showed the best effect, the results were noticed with a minus sign and, in those cases in which placebo II had the best effect, the results were indicated with a plus sign. Where there was no difference in the 6-hour periods, a 0 (zero) was marked and these results were not included in the statistical testing. The plus and minus signs for all 36 patients were added separately, the sum being 83 minuses and 62 pluses. The difference was significant (level of significance: .10).

In this investigation, the parameter-free Sign test was used. This does not require normal distribution of material, nor any internal norm relationship of the index figures for the different patients. The strength of the Sign test is only 95 % of that of a parameter test.

TABLE 2

Differences in the antipruritic effects of R 516 and placebo. For each of the 36 patients paired comparisons were made between the itching indexes for 6-hour periods, during which the respective preparations were given under the same prevailing conditions. The sum of the results was tested with the aid of the Sign test.

	Least itching during R 516 period = minus sign	Least itching during placebo II period = plus sign	Statistical testing (Significance level = .10)
Expected sign distribution for equal effect of R 516 and placebo	72.5	72.5	----
Sign distribution in present series	82	62	Significant

C. Side Effects of R 516.

The patients were questioned regularly regarding the possible occurrence of side effects such as tiredness, nausea, intestinal disturbances, headaches, dizziness, etc. In no case was

it found necessary to withdraw the preparation because of side effects. However, some patients stated that they felt slightly sleepy and tired.

SUMMARY

Using a special double-blind method, comparative experiments were carried out with a new antihistamine drug R 516 (Glanil®) and with placebo in order to study the antipruritic effect in patients suffering from skin diseases, eczema in particular.

Itching was studied in 17 patients receiving only placebo therapy in connection with hospitalization. Itching regressed rapidly during the first two days, and more slowly during the subsequent days. For this reason, the double-blind investigation with R 516 was postponed until two days had been spent in hospital. The investigation, which involved 36 patients, showed with 90 % significance, that the low daily dose of 15 mg R 516 gave an antipruritic effect in patients with dermatoses accompanied by itching. The only side effect noted was a slight degree of tiredness.

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