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EVALUATION OF SLOW-RELEASING DIPHENYLPYRALINE IN CHRONIC URTICARIA AND VARIOUS KINDS OF DERMATITES

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Diphenylpyraline (formula see Fig. 1) is an antihistaminic agent which was synthesized as early as 1949. It was demonstrated to have a high antihistaminic activity and low toxicity in clinical and animal experiments (3, 5).

In spite of a high antihistaminic activity, diphenylpyraline was not adopted into general use because of its short term activity so that it had to be administered frequently. *Andre et al.* (1961) reported, however, that a porous tablet compressed in a plastic cell produces a prolonged and even concentration in blood. They also observed that diphenylpyraline in this form of a sustained release tablet acts very effectively upon allergic rhinitis (1). Furthermore, it was observed that diphenylpyraline compressed in a plastic cell had a strong inhibitory effect upon histamine applied to the skin by iontophoresis (2).

The purpose of this study was to demonstrate the antihistaminic effect of diphenylpyraline upon a group of patients suffering from chronic, "non-allergic" urticaria. Non-allergic urticaria here means cases of urticaria in which no hypersensitivity to any food or drug could be demonstrated and in which no focal infections could be observed.

This kind of chronic urticaria is not a common disease but

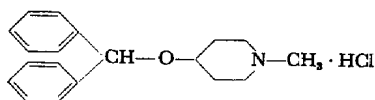


Fig. 1.

4-diphenyl-methoxy-1-methylpiperidin hydrochloride.

it is of long duration and the results of the treatment vary to a great extent, both with antihistaminic preparations and cortisone. In addition to this, the aim of this experiment was to study the pruritus suppressing effect of diphenylpyraline in common acute and chronic dermatites of various origins. Besides the antihistaminic effect, the study was designed to find the potential side-effects of diphenylpyraline.

MATERIAL AND METHODS

The material consisted of 40 patients, 20 of whom were suffering from chronic "non-allergic" urticaria (Group I) and 20 from other pruritic conditions (Group II).

Group I

The 20 patients affected by chronic urticaria consisted of 13 women and 7 men. Their ages ranged from 4 to 51 years. No agent provoking urticaria could be found in ten cases. Cold weather provoked skin manifestations in four patients, while urticaria appeared in connection with sweating in three cases. The disorder was probably caused by psychic factors in the three remaining cases.

All the patients had been suffering from urticaria at least for two months, nine patients a year or longer. Simultaneously, chronic vasomotor rhinitis occurred in five patients and maxillary sinusitis considered allergic, in one. Eighteen patients had previously been given one or more antihistaminic preparations, which had given some transient relief in 5 cases. There was no effect in 13 cases.

The patients of this group were given 5 mg of diphenylpyraline twice a day for two weeks' and subsequently 5 mg every evening. A placebo was tried in five patients for one week after 2 weeks' diphenylpyraline treatment.

The patients were mainly examined and treated in the outpatient department. Twelve patients were admitted to the hospital for a short-term treatment. To follow the results of the treatment and to find the potential side effects the patients were examined every 1 to 2 weeks.

The blood cell count, serum glutamic pyruvic transaminase (SGPT) and serum creatinine of all the 20 patients were examined both at the beginning of the treatment and after it. These samples were taken from ten patients also after 1, 2 and 4 weeks' treatment.

Group II

Twenty patients, 11 female and 9 male, were affected by various kinds of dermatites. Their ages ranged from 12 to 71 years. The following diagnoses were made:

- Atopic dermatitis	7
- Allergic contact dermatitis	8
- Toxic contact dermatitis	4
- Dermatitis herpetiformis	1

The duration of the skin manifestations was less than 2 months in 8 patients and longer in others.

The patients in this group received 5 mg of diphenylpyraline twice a day for two weeks in addition to various kinds of local treatment. Subsequently, eight patients were given a continual maintenance dosage of 5 mg $\times$ 1. The patients were examined every 1 to 2 weeks.

RESULTS

Group I

Symptoms disappeared during diphenylpyraline treatment in 11 patients out of the 20 suffering from chronic urticaria. Urticarial papules ceased to appear on the average one week after the beginning of the treatment.

The treatment could be terminated in seven of these patients; no reactivation of urticaria was recorded during the 2 months' observation period in the patients. The average period of treatment was about one month. (Table 1) Five of these patients had earlier been given some antihistaminic preparation — no relief was observed in three, moderate relief occurred in two.

Four patients had no symptoms during continual treatment, but the administration of the drug could not be terminated during the test, because new wheals appeared as soon as the treatment was withdrawn. The symptoms were suppressed by a maintenance dose varying between 2.5 to 5 mg/die. The

TABLE I
*The Effect of Diphenylpyraline in Twenty Patients with Chronic Urticaria
 Compared to Previous Antihistaminic Treatment and Agents Provoking Urticaria.*

The effect of diphenyl- pyraline	Number of patients	A. The effect of previous antihistamines			B. Agents provoking urticaria			
		No effect	Moderate	No previous treatment	Cold	Sweat	Psychic factors	No provoking agents
No symptoms after treatment	7	3	2	2	2	—	1	4
No symptoms with prolonged treatment	4	3	1	—	—	1	—	3
Reduction of symptoms	7	5	2	—	2	1	2	2
No effect	2	2	—	—	—	1	—	1
Total	20	13	5	2	4	3	3	10

period of treatment ranged from 1 to 6 months. One of the four patients had obtained temporary relief after previous administration of antihistamines, but any earlier treatment had proved ineffective in the rest.

The symptoms decreased considerably in seven patients. One of them stopped taking the medicine after a month after which he had fewer symptoms than earlier. The treatment of the others was continued with a maintenance dose of 5 mg/die; the period of the treatment ranged from 1 to 4 months. Earlier antihistaminic medication had produced no relief in five patients, and in two the effect of a previous treatment had been rather similar to that of diphenylpyraline.

Urticaria remained unchanged in two patients during the 4 to 6 weeks' treatment. Previous antihistaminic treatment had also proved unsuccessful in both of them.

Analysis of the background of the chronic urticaria and results obtained with diphenylpyraline is presented in part B of the Table 1. Of the patients in whom urticaria was provoked by cold, 2 were free after diphenylpyraline treatment. The period of the treatment was one month. Decrease of the symptoms was noticed in two patients, but formation of urticarial papules was not completely inhibited by the treatment. All the four patients suffering from cold urticaria had had symptoms at least one year.

Urticaria was provoked by sweating in three patients who had been affected for 1, 4, and 10 years. Antihistamines administered previously had produced no relief. No symptoms were observed in one patient, and those of the second patient were decreased significantly by diphenylpyraline but in the third patient urticaria remained unchanged.

Psychic factors seemed to provoke formation of urticaria in three patients. No symptoms occurred in one of the three who had suffered from urticaria without interruption for two years, during a diphenylpyraline treatment of one month. Moderate relief was observed in the other two; they had fewer symptoms due to uninterrupted treatment.

No urticaria provoking agent could be found in ten pa-

tients. No symptoms occurred in four of them after the treatment, while three patients remained without manifestations when the medication was continued. The symptoms were decreased by uninterrupted treatment in two patients but diphenylpyraline had no relieving effect upon one.

Simultaneously, in addition to chronic urticaria, five patients were affected by chronic vasomotor rhinitis. The symptoms of rhinitis were suppressed in all of them by uninterrupted diphenylpyraline treatment. One patient had chronic maxillary sinusitis considered allergic. No symptoms were observed in this patient during the treatment.

The effect of a placebo was tried in five patients for one week after two weeks' diphenylpyraline treatment. The patients were told they were having a slightly milder drug. The symptoms had been suppressed by the foregoing diphenylpyraline treatment in four patients. Urticaria remanifested itself in three of them during the placebo treatment; one of them experienced no symptoms and was subsequently symptomless without any medication. The two week's diphenylpyraline treatment was of some effect in one patient, because the symptoms decreased considerably. Urticarial manifestations increased markedly during the week of placebo treatment, the condition of the patient being the same as before the diphenylpyraline treatment.

Group II

The effect of diphenylpyraline on pruritus in 20 patients affected by various kinds of dermatitis is shown in Table 2. Pruritus was completely suppressed in 9 and was considerably alleviated in 7 patients. No change was observed in 4 patients.

The effect of diphenylpyraline on pruritus was independent of the etiology of dermatitis. The effect was good in three, moderate in two, and poor in two patients suffering from atopic dermatitis. The period of treatment was about one month. Most of these patients had previously been administered other antihistaminic preparations the effect of which had been about the same.

TABLE 2

The Effect of Diphenylpyraline on Pruritus in Twenty Patients with Various Kinds of Dermatitis.

	Number of patients	The effect of diphenylpyraline		
		Good	Moderate	Poor
Atopic dermatitis	7	3	2	2
Allergic contact dermatitis	8	2	4	2
Toxic contact dermatitis	4	3	1	—
Dermatitis herpetiformis	1	1	—	—
Total	20	9	7	4

Pruritus was completely suppressed in two patients suffering from allergic contact dermatitis, the effect was moderate in four and poor in two patients. The result was good in three and moderate in one patient suffering from toxic contact dermatitis. The material consisted also of a patient affected by dermatitis herpetiformis, who due to a serious renal disorder could not have sulfones. Pruritus was effectively suppressed but the formation of vesicles was not inhibited by diphenylpyraline.

Side-effects

Minor side-effects were observed in 5 patients four of which belonged to group I and one to group II.

Four patients suffered from mild sleepiness that did not disturb the treatment. Nausea occurred in one of them simultaneously. Furthermore, one patient complained of nausea that did not disappear after the completion of the treatment. Therefore it was not certain that nausea was attributable to diphenylpyraline.

No effect of diphenylpyraline on blood cell count was

indicated by laboratory tests, nor was there increase of SGPT or creatinine during the treatment in the 20 patients affected by chronic urticaria.

DISCUSSION

The etiology of chronic urticaria is seldom formed by a clear immunological reaction or a reaction due to direct liberation of histamine as is the case in acute urticaria. The effect of antihistaminic preparations in chronic urticaria varies, and is not exclusively based on histamine antagonism. However, an antihistaminic preparation that can control urticaria is often discovered. Pruritus should also be suppressed by a good antihistamine and a prolonged treatment ought to be possible without side-effects. Although spontaneous, sudden recoveries occur in chronic urticaria, the chronic urticaria due to its long duration is more suitable for evaluating the antihistaminic activity of a preparation than an acute urticaria which is a spontaneously self-curing disease.

The effect of diphenylpyraline upon chronic urticaria has been previously tested by *Spapen* (1969) with a porous plastic tablet. His material consisted of 17 patients that were part of a more extensive clinical trial. The results are reported to have been very good in 8, good in 6, and moderate in 3 cases; agents provoking urticaria, duration of the disease or effect of antihistaminic drugs possibly used in the past are not mentioned (4).

This study of 20 patients affected by chronic, "non-allergic" urticaria showed that diphenylpyraline presents high activity in suppressing urticaria. The treatment proved to be most successful in those, in whom no urticaria provoking agent could be observed. However, the effect was very good also in cold urticaria in which antihistamines do not always succeed in inhibiting formation of urticarial papules.

In treating various kinds of dermatites, allergic or non-allergic, antihistamines are commonly used due to their anti-pruritic activity. The treatment is palliative and contributes

to the effect of a simultaneous, local treatment accelerating it at the same time. The effect of antihistamines on pruritus in these patients varies being usually between good and moderate. The effect of diphenylpyraline in form of a porous plastic tablet is, according to this study, the same and corresponds also to the results obtained by *Spapen* (4).

SUMMARY AND CONCLUSIONS

Diphenylpyraline in a porous plastic tablet was tried in 40 patients, 20 of which were affected by chronic, "non-allergic" urticaria and 20 by etiologically dissimilar dermatites.

The dosage was 5 mg of diphenylpyraline twice a day for two weeks and subsequently 5 mg daily, if long-term treatment was necessary.

All the symptoms were suppressed by diphenylpyraline in 11 and reduced considerably in 7 patients suffering from chronic urticaria. No alleviation was observed in 2 patients. The result is very good considering that most patients had been given other antihistamines in the past without any effect.

Pruritus was controlled rather effectively by diphenylpyraline in various dermatites.

Minor side-effects, that did not disturb the treatment, were observed in 5 patients.

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