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Antiserotonin-antihistamine agents in allergic diseases — Clinical evaluation of cyproheptadine

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With 2 figures

Recently a chemical compound, 1-methyl-4-(5-dibenzo-[a,e]cycloheptatrienylidene)-piperidine (cyproheptadine), was synthesized which presents the characteristic of being at the same time a potent antihistamine and an antiserotonin substance with similar activity to that of lysergic acid diethylamide (*Stone* et al. [1]).

It is well known that histamine plays an important role in the phenomena of allergy and anaphylaxis. However, as *Humphrey* and *Jaques* (2), *Rocha e Silva* (3) and numerous authors have shown (4, 5, 6, 7), especially in anaphylactic reactions several other pharmacodynamically active substances in addition to histamine, such as 5-hydroxytryptamine or serotonin, bradykinin, etc., are released. Although the role that serotonin plays in allergic reactions is not clear, nevertheless it has been of considerable interest to investigate clinically a drug that has combined antihistamine and antiserotinin activity.

The purpose of the present investigation was to study the effect of cyproheptadine on two types of allergic diseases: asthma, in which antihistaminic agents have little favorable effect, and urticaria, in which the antihistamines exert considerable therapeutic effect.

Case material and methods

In order to study the effect of the drug for several days or weeks, for the present investigation, diseases of a chronic type, such as asthma, chronic urticaria and papular urticaria, were preferred. The allergic nature of the disease was established in each patient by a thorough clinical history, by skin tests or by the two procedures combined.

The patients were divided into various treatment groups in order to compare the effect of cyproheptadine, on the one hand, with antihistamines with well recognized activity and, on the other hand, with corticoids. In addition, in some groups there was a period in which only a placebo was administered.

Patients with asthma. A total of 61 patients were divided into 5 groups. The age, sex, length of illness and other data are given in table I. Of the 20 patients in the group treated with prednisolone, 10 received this drug for the whole period of study; the other 10 patients received only a placebo during the first 10 days and then prednisolone. Cyproheptadine and antihistamines were administered only for a period of 10 days, while the corticoids were given for 20 days. When, in spite of treatment with any of the drugs studied, patients suffered a severe attack of asthma, they were permitted to have inhalations of isoproterenol in aerosol form.

To evaluate the intensity of the crisis and the asthmatic attacks as well as the effect of the drugs in question, we proceeded in a manner similar to the technic adopted in a previous study (*Naranjo* [8]). Each patient or else the mother, if the patient was a child, was instructed

to keep a daily record of the severity and duration of the attacks. The severity was classified in three grades: Grade I, when the dyspnea was moderate and did not interfere with the performance of the usual work or, in children, did not prevent them from playing freely and, during the night, the patients was not obliged to adopt an orthopneic posture; Grade II, when dyspnea necessitated the occasional interruption of work and during the night necessitated the adoption of an orthopneic position and, in the case of children, when dyspnea prevented them from participating in fatiguing games; and Grade III, when the intensity, frequency and duration of attacks of dyspnea made it necessary for the patients to stay in bed. In children, especially in those in whom coughing is a frequent, persistent symptom, this symptom was also considered for the evaluation of the degree of asthma.

For the diagrammatic presentation of the effect of the drugs, the "asthmatic index" was established, which is only the product of the degree of asthma by the length of the attacks, in hours per day.

Patients with chronic urticaria. We selected 53 patients with papular urticaria or chronic urticaria, and they were divided into 5 treatment groups. The age and conditions previous to treatment may be seen in table II.

Half of the patients of the groups on diphenyhydramine, cyproheptadine and dexamethasone received one of these drugs, respectively, for the entire period of study; the other half received the drug for the first 10 days and this was replaced by a placebo during the following 10 days, with a return to the initial treatment during the final 10 days.

Table I

Asthmatic patients and their condition[1]) previous to treatment

Case material	Chlorprophenpyridamine	Promethazine	Cyproheptadine	Prednisolone[2]) A	Prednisolone[2]) B	Dexamethasone
Total patients .	8	8	10	10	10	15
Sex						
Male	4	5	5	5	4	7
Female	4	5	5	5	4	8
Age						
< 5 years . .	2	2	2	1	2	3
5–20 years . .	3	3	4	5	4	6
20–50 years . .	3	3	4	4	4	6
Duration present attack						
< 5 days . . .	3	3	4	4	3	6
5–10 days . . .	3	4	4	4	6	8
> 10 days . . .	2	1	2	2	1	1
Intensity attack[1]						
Grade I	2	1	3	3	3	4
Grade II . . .	3	3	3	4	4	5
Grade III . . .	3	4	4	4	3	6
Average „asthmatic index"[1])	7.9	8.2	7.6	7.8	8.0	8.1

[1]) For the form of evaluation, see text.

[2]) Group A received only prednisolone. Group B received placebo for 10 days and prednisolone for the next 10 days.

The evaluation of the severity of the disease as well as of the effect of the drugs was conducted by a technic similar to that used in previous studies (*Naranjo* [8, 9]). Consideration was given to the following symptoms or signs: pruritus, erythema and papules, as well as the extensiveness of the skin affected. Each symptom or sign was assigned a value of 1 to 4, and 4 grades of severity were established: Grade I, when the sum of the individual values was up to 4; Grade II, from 4 to 8; Grade III, from 8 to 12 and Grade IV when this sum was more than 12. The papular manifestation was evaluated objectively on areas of 2 sq. cm. which, for papular urticaria, were preferably on the forearms and sacrococcygeal region, which are sites for the occurrence of abundant papules. Lesions due to scratching of the papules or erythema served as an objective index of the severity of the pruritus, although subjective information from each patient was also considered.

Both for the group of asthmatics and for those with urticaria, their clinical condition was re-evaluated every 2 to 4 days, and in the case of cyproheptadine special attention was given to the appearance of possible side effects.

Drugs used. The following drugs were investigated: Cyproheptadine as the hydrochloride (Periactin, Merck Sharp & Dohme); diphenhydramine as the hydrochloride (Benadryl, Parke Davis); chlorprophenpyridamine as the maleate (Chlor-Trimeton, Schering Corp.); promethazine (Phenergan, Specia); prednisolone (Deltacortril, Pfizer) and dexamethasone (Decadron, Merck Sharp & Dohme).

Table II

Patients with urticaria and their condition[1]) previous to treatment

Case material	Chlor-prophen-pyrid-amine	Pro-metha-zine	Diphen-hydr-amine	Cypro-hep-tadine	Dexa-metha-sone[2])
Total patients . .	10	8	8	15	12
Sex					
Male	3	3	3	6	4
Female	7	5	5	9	8
Age					
< 5 years	6	6	5	8	7
5–10 years	3	2	2	5	3
> 10 years	1	0	1	2	2
Duration urticaria					
< 1 month	4	3	4	8	4
1–2 months . .	2	3	3	5	5
> 2 months . . .	2	2	1	2	3
Intensity[1])					
Grade I	1	1	1	3	2
Grade II	3	2	3	3	3
Grade III	4	4	3	6	4
Grade IV	2	1	1	3	3
Average "urticarial index"[1])	9.5	8.9	8.6	9.1	9.3

[1]) For the form of evaluation, see text.
[2]) In this group there was an intermediate period of 10 days, during which half the individuals received only placebo.

Table III

Dose administered according to the age and clinical response of the patients

Drug	< 5 years mg.	5—10 years mg.	> 10 years mg.
Chlorprophenpyridamine	5—10	12—20	24—40
Promethazine	8—16	20—50	50—75
Diphenhydramine	20—40	50—100	100—150
Cyproheptadine	4 6	6—8	12—20
Prednisolone (initial dose)	5—7.5	7.5—15	15—25
Dexamethasone (initial dose)	0.6-1.0	1.0 1.6	2.4 - 4 0

Dosage. We tried to establish the dose of each drug, as may be seen in table III, on the one hand, in relation to the age of the patient and, on the other, in relation to the therapeutic response that was obtained during the first 3 days of treatment. The daily dose and its fractional administration had to be adjusted to the content of active drug of the respective pharmaceutical form. With the antihistamines and cyproheptadine we tried to determine, during the first 3 days of treatment, the most effective dose, and this was continued during the period of study. On the other hand, with the corticoids the daily dose was decreased by 20 to 25% every 5 days. In all cases the daily dose was given in 3 or 4 fractional doses. To children less than 5 years of age, when available the drug was administered in the form of a syrup; to the others, in the form of tablets or capsules.

Results

Asthmatic patients. Cyproheptadine, especially in children and particularly in those who had not received previous antihistamine medication, produced rapid lessening of the symptoms, particularly of paroxysms of coughing; on succeeding days the improvement did not advance; the asthmatic attacks persisted, although somewhat lessened, and in only one of the 10 patients the asthmatic crisis disappeared within the 10 days of treatment. In adults the improvement was very slight, but also in these persons when attacks of coughing occurred, their severity decreased; on the other hand the attacks of dyspnea continued to occur on succeeding days. As may be seen from figure 1, on the average, the asthmatic index decreased about 50% during the first 5 days and became stable subsequently.

The 2 antihistamines studied in this clinical series, chlorprophenpyridamine and promethazine, in the doses used gave therapeutic results inferior to those of cyproheptadine, especially chlorprophenpyridamine, which produced slight reduction of the symptoms, solely in children giving a decrease of the asthmatic index of only about 17%. It was precisely because of the results that the administration both of cyproheptadine and of antihistamines was suspended after 10 days of treatment.

In the group of patients who received placebo there was slight lessening of the symptoms, which did not exceed 10% diminution of the asthmatic index during the first 3 days of treatment; on the succeeding days the symptoms returned to their initial value or were exacerbated.

In the patients to whom one of the 2 corticoids was administered, a consistent improvement was observed in the course of 20 days of treatment. Also, in these groups the improvement was greater in children than in adults. In the majority of

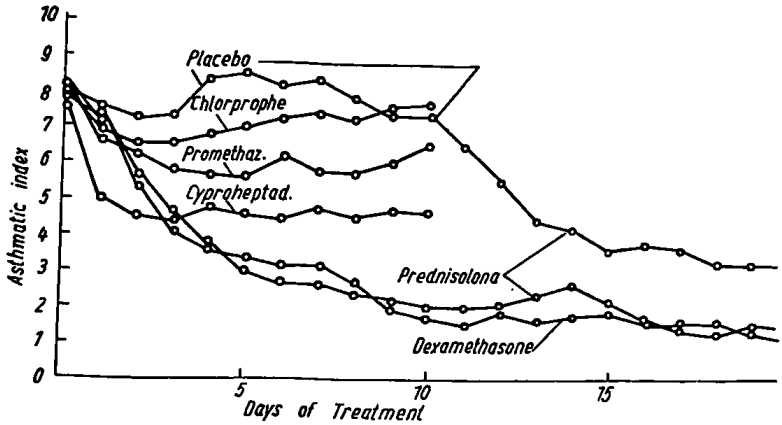

Fig. 1. Effect of various drugs in the symptomatic treatment of asthma. The improvement of the patients appears as a diminution of the "asthmatic index".

the children all the symptoms disappeared before 20 days. The asthmatic index was reduced approximately 80 %. The clinical results abtained with the 2 corticoids were very similar, but doses of prednisolone 6 to 8 times greater than those of dexamethasone were required.

Patients with urticaria. Cyproheptadine produced considerable attenuation of the pruritus after the first 24 hours. In regard to this effect, the result was very similar to or better than that obtained with promethazine and superior to that obtained with the other 2 antihistamines studied. Compared to the antihistamines, cyproheptadine, figure 2, produced a more rapid and better fall in the urticarial index. With regard to the papular manifestations, the disappearance of papules already existing was more rapid with cyproheptadine than with chlorprophenpyridamine or diphenhydramine, and likewise cyproheptadine was superior in preventing the appearance of new papules. In the majority of the patients all the pathologic manifestations had disappeared about the 20th day of treatment; but in 25 % of them the improvement did not progress during the last 10 days of treatment.

With dexamethasone the alleviation of the pruritus during the first few days was less than with cyproheptadine or the antihistamines. However, the improvement was consistently progressive, and before the 30th day the pathologic manifestations had disappeared in all the patients.

In the 3 subgroups in whom an intermediate period of treatment with a placebo was introduced, there was rapid worsening in those who had been subjected to treatment with diphenhydramine and cyproheptadine. In those who had had corticoid treatment, while it is certain that there was also exacerbation of the pathologic manifestations, it was of much less degree than that of the other 2 subgroups. Upon restitution of the active treatment, the symptoms again diminished similarly as in the initial period.

Side effects. In the majority of patients, especially in those who had not been subjected to antihistamine treatment, cyproheptadine produced somnolence during the first few days of treatment, but it was not necessary in any of them to decrease the dose or interrupt the treatment. This side effect was less than that observed with

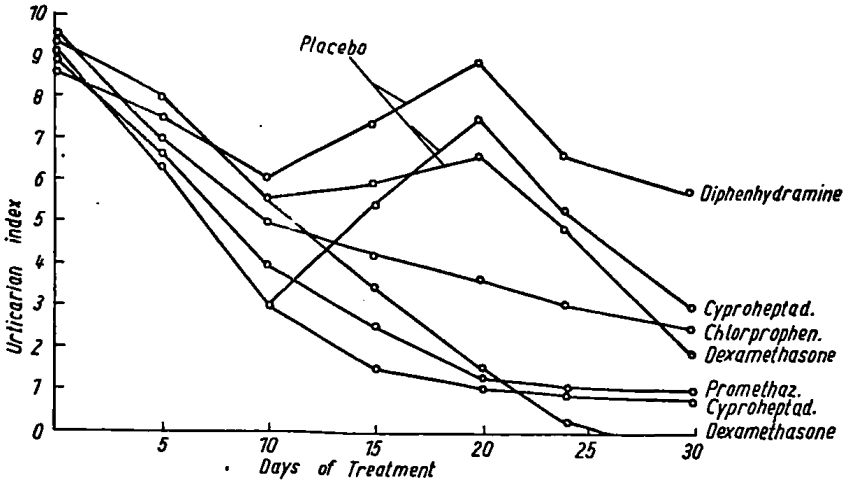

Fig. 2. Effect of various drugs in the symptomatic treatment of papular urticaria and chronic urticaria. The improvement of the patients appears as a diminution of "urticaria".

promethazine or with diphenhydramine but greater than that observed with chlorprophenpyridamine. Likewise, in the majority of the patients cyproheptadine was found to produce a sedative and tranquilizing effect. In addition to somnolence, two of the 25 patients complained of a sensation of stupefaction or confusion.

In the majority of the patients cyproheptadine produced an increase in appetite, and in children, in whom the weight was observed, this was found to increase. In children who were treated for 30 days, there was an increase of 328 g. ± 38 g.; on the other hand, in children who received antihistamines for a like period of time, there was an increase of only 158 g. ± 21 g. ($P = < 0.05$).

Discussion

The result obtained with cyproheptadine in the symptomatic treatment of asthma, although greater than that of 2 quite potent antihistamines, was not of great practical value, especially in adults. Although histamine certainly plays some part in the pathogenesis of allergic asthma, the pathologic phenomenon is much more complex than a simple reaction to histamine and, as is known, antihistamines have little value in the treatment of this disease. The fact that cyproheptadine, notwithstanding its high antiserotonin property, is also not very effective in the treatment of asthma would reveal indirectly that neither is serotonin an essential factor in the pathogenesis of this disease. These results would confirm indirectly those of *Brocklehurst* (10), according to which there is little or no liberation of serotonin in the human bronchi.

According to laboratory studies (*Stone* et al. [1]) cyproheptadine is a potent antihistamine useful in urticaria and especially in the suppression of pruritus. The antipruriginous and local anesthetic effect is, however, not closely related to the antihistamine effect (*Naranjo* and *de Naranjo* [11]). It is possible, then, that the clinical effects produced by cyproheptadine in urticaria are not due only to the antihistaminic action of this substance but rather also to its antiserotonin action.

Some of the antihistamines, principally the phenothiazine derivatives, possess a certain antiserotonin activity. In cyproheptadine this reaches a high level, and there-

fore its is to be considered that with this new drug a new phase of laboratory as well as clinical experimentation is opened, whence there will be a new pharmacodynamic family: a family of antihistamine-antiserotonin drugs.

Summary: Cyproheptadine, a drug that possesses both antihistamine and antiserotonin activity, was studied in various allergic diseases in comparison with a placebo, antihistamines and corticoids.

In asthmatic patients it produced more marked relief in the first few days of treatment than subsequently. Cyproheptadine alone was not capable of completely arresting an asthmatic crisis in any of the patients. In a comparative test with two antihistamines (chlorprophenpyridamine and promethazine) and two corticoids (prednisolone and dexamethasone), cyproheptadine was more effective than the antihistamines (fewer number of days of asthma and shorter duration of attacks), but upon long-term treatment it was inferior to the corticoids, with which the asthmatic crisis could be completely suppressed.

In chronic urticaria and papular urticaria cyproheptadine had an antipruriginous effect superior to that of the antihistamines. In comparison with the corticoids, cyproheptadine gives considerable inmediate relief, but for long-term treatment the corticoids were superior

The side effects of cyproheptadine were generally mild, and the most frequent one was somnolence. It was also observed, especially in the children, that the appetite was increased and there was an increase in body weight.

Zusammenfassung: Es wurden Versuche mit „Cyproheptadin" gemacht, einer Substanz sowohl mit Antihistaminwirkung wie auch Antiserotoninwirkung, und Vergleiche bei verschiedenen allergischen Affektionen angestellt mit Plazebos, Antihistaminen und Kortikoiden. Bei Asthmatikern führte die Verbindung zu einem besseren Ergebnis in den ersten Behandlungstagen als in den folgenden. Bei keinem Patienten konnte Cyproheptadin allein den Asthmaanfall völlig beheben.

Im Vergleich mit zwei Antihistaminen (Chlorprophen-pyrimidin und Promethazin) und mit zwei Kortikoiden (Prednisolon und Dexamethason) war Cyproheptadin wirksamer als die Antihistamine (weniger Asthmatage, kürzere Anfälle), aber bei längerer Behandlung war es den Kortikoiden unterlegen, die die völlige Unterdrückung der asthmatischen Anfälle ermöglichten.

Bei chronischer und papulöser Urtikaria zeigte Cyproheptadin sich der antipruriginösen Wirkung der Antihistamine überlegen. Verglichen mit den Kortikoiden wurde eine beträchtliche Sofortwirkung festgestellt, bei längerer Behandlung die Überlegenheit der Kortikoide.

Die Nebenwirkungen des Cyproheptadins waren allgemein leichter Art, am häufigsten wurde Schläfrigkeit beobachtet. Besonders bei Kindern wurde Appetitssteigerung mit Anstieg des Körpergewichts festgestellt.

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Addenda. 1) Recently we began a new series of studies with a combination of cyproheptadine 4 mg. and dexamethasone 0.25 mg. per tablet. The clinical results seem superior to those obtained with each of these drugs separately; however, definite conclusions can be obtained only after a more extensive study.

2) After this manuscript had been prepared, a paper appeared entitled "Clinical use of a new Antihistamine and Antiserotonin drug: Cyproheptadine", by *T. Bodi* et al. (An. Allergy **19**, 4, 386 [1961]). The results, although evaluated by a different method, are essentially in agreement with ours.

ALLERGIE UND ASTHMA
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