A CLINICAL TRIAL OF CYPROHEPTADINE ('PERIACTIN')

(A new antihistamine, antiserotonin and antipruritic agent)

by

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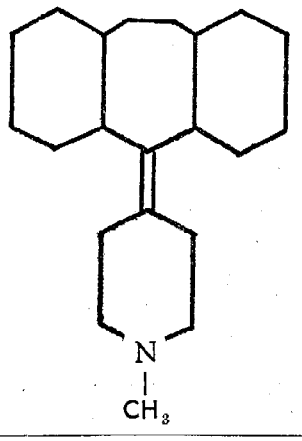
Since the discovery of antergan (N-phenyl-N-benzyl-N-dimethyl-ethylene-diamine), a large number of clinically effective antihistamines have been developed. These drugs constitute valuable agents in our therapeutic armamentarium, particularly for use in anti-allergic therapy. But the ever increasing number of these antihistamine drugs, have produced some confusion in the mind of physicians regarding the choice of a preparation suitable to the patient. Goodman and Gillman[1] mention that of these large number of antihistaminic drugs, little distinction can be made between them on the basis of efficacy as histamine antagonists. They vary somewhat with respect to potency, dosage, relative incidence of side effects, and the types of preparations available. Naturally, the physician is desirous of choosing the particular antihistamine which will assure him the greatest opportunity of therapeutic success with the minimal chance of side actions. Unfortunately, no antihistamine drug is outstanding in this respect. The difficulty lies in the quantitative assessment of both therapeutic efficacy and incidence and severity of side effects in a large number of drugs studied by many investigators. Laboratory investigations have been of little help, as there is no close correlation betweon potency of an antihistamine as measured by the usual laboratory techniques and clinical effectiveness.

Recently a new antihistamine and antiserotonin drug, cyproheptadine hydrochloride (Periactin), was introduced to us by Messrs. Merck Sharp & Dhome. The therapeutic trials of this compound are favourably reported by Bodi and others[2]; Welsh[3] and Sperber[4] in western literature.

PHARMACOLOGY OF CYPROHEPTADINE

Cyproheptadine is a new antihistamine drug with the following chemical strucure :



'PERIACTIN'

.HCl.H_2O

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It is methyl-4-(5-dibenzo-(a, e)-cycloheptatrienylidine-piperidine hydrochloride monohydrate. There is no sulfur or nitrogen in the ring system and the drug is not a phenothiazine. This compound has no resemblance to the ethylamine side chain of the other antihistaminic compounds. However, as stressed by Robson and Keele[6], mechanism of action of antihistamines by competition with histamine for attachment to the receptor cells is not proved as some of the antihistamine compounds have no resemblance to the ethylamine side chain which is supposed to resemble the structure of histamine.

Pharmacological studies suggest that cyproheptadine possesses a broad spectrum of action[6]. As a potent antihistamine, it antagonises the broncho-constrictor, spasmogenic and vasodepressor effect of histamine in various animals tested. The drug protected against passive and active anaphylaxis and, in addition blocked histamine induced gastric secretion in the dog, a property ordinarily lacking in antihistamine agents. Its antihistamine potency is comparable to that of chlorprophenpyridamine maleate and pyrilamine[6].

The compound showed strong antiserotonin activity[6,7]. It antagonised a wide variety of serotonin effects such as the broncho-constrictor effect in guinea pigs, the spasmogenic effect in isolated rat uterus, the vascular action in dogs, increased capillary permeability and the lethal effect in Hemophilus pertussis-treated mice. It compared favourably with other serotonin antagonists. It seemed to be as active as lysergic acid diethylamide (LSD^{25}). Neither cyproheptadine or LSD^{25} blocked serotonin induced intestinal hyperactivity in the unanesthetized dog.

It is superior to BMS (1-benzyl-2-methyl-5-hydroxytryptamine) and BAS (1-benzyl-2-methyl-5-methoxytrypamine).

The dual antagonism of cyproheptadine to serotonin and histamine makes it a valuable therapeutic agent with a broader spectrum of activity than most conventional antihistamine drugs. Hence we were prompted to evaluate this agent in various allergic disorders, as the known participation of histamine and the possible role of serotonin in allergic states is known.

It is recognised that antihistamines are not uniformly effective in any given allergic disorder, and some of these syndromes are quite resistant to such therapy. Therefore, it is likely that formation or liberation of substances other than histamine plays a role in the allergic phenomena. These substances may potentiate or produce effects similar to histamine. Antihistamines may not influence these effects.

Serotonin is a substance which is receiving increased attention as a possible amine involved in certain types of hypersensitivity diseases[8]. In many species, serotonin occurs in the same tissues as histamine. Pharmacologically it acts like histamine in many ways. Release of serotonin from rabbit platelets during in vitro anaphylactic reactions has been demonstrated[9]. A recent report suggests the etiologic importance of serotonin, released in a physiologically active form, in

rabbit.[10] More recently, cyproheptadine was found to be effective in suppressing, and attenuating microscopic lesions of periarteritis and panarteritis produced by reversed bovine serum subanaphylactic sensitization.[7] It is of interest that potent antihistamines like tripelennamine and diphenhydramine were ineffective in modifying the development of passive sensitization vasculitis.[11]

The depressant action of cyproheptadine was evident in studies on cats and monkeys. In these animals the response was similar to chlorpromazine, but in some ways resembled that of scopolamine. In low doses, it has a stimulatory effect in rats, resembling that of the amphetamines. It exhibits both anti-convulsant and anti-tremor properties in mice, the first by its ability to antagonise convulsions caused by the injected nicotine and appropriate electrical stimulation, the second by its antagonism of tremorine. When administered in large oral doses or parenterally, cyproheptadine produced hyperglycemia in dogs and mice.

METHOD & MATERIAL

This report is concerned with a short clinical trial of this compound in 51 cases. The cases selected were mainly those in which allergic causative mechanisms were concerned or those in the non-allergic group where severe pruritis was a prominent feature. The intention was to assess clinically the anti-allergic and anti-pruritic effects of the drug.

Cyproheptadine ('PERIACTIN') was given in tablet from (4 mg.) in a dose of 1 tablet T. D. S. or B. D. for adults and 2 mg. T. D. S. or Q. D. S. in children. Additional non-specific appropriate local therapy was given to all the patients. Treatment was discontinued after a trial of 10 days in those cases which did not show material benefit.

Anti-allergic Effect of the Drug: These effects were assessed in cases of acute urticaria, angioneurotic oedema, atopic dermatitis, allergic dermatitis, prurigo, infectious eczematoid dermatitis, drug eruptions, contact dermatitis and Henoch-Schonlein syndrome. In all these conditions, the causative mechanism is invariably of an allergic nature. In some of these skin conditions, the mechanism is dermal in origin-wheal type and in others, epidermal in origin delayed vesicular type. It is well known that antihistaminic drugs have a more pronounced effect in the former and less or no effect in the latter variety. Some of these cases presented clinically a combination of both a dermal-vesicular type of manifestations. The results were assessed objectively by the subsidence of exudative lesions and considered good if relief was more than 70%, fair if between 40–70% and poor if there was less change or no change.

Table I shows the results.

DISCUSSION

Acute Urticaria: All cases in this group responded well. The patients had complete relief of their symptoms, and being of an acute nature, the temporary hypersensitive phase came under control rapidly. Four cases came under control in 2 days, 6 cases within a week and 2 cases in the course of 10 days.

Angioneurotic oedema: Subsidence of oedematous swellings was seen in 6 hours and total clearance of lesions in a day's time.

TABLE I

	Good	Fair	Poor	Total
1. Acute urticaria	12	–	–	12
2. Angioneurotic oedema	5	–	–	5
3. Allergic Dermatitis	3	1	1	5
4. Atopic Dermatitis	–	–	2	2
5. Contact Dermatitis	2	–	–	2
6. Prurigo	–	2	2	4
7. Drug Eruption	5	–	–	5
8. Infectious Eczematoid Dermatitis	2	–	–	2
9. Henoch-Schonlein syndrome	3	–	–	3
	32	3	5	40

Allergic dermatitis: From this heterogenous group, 3 cases of acute generalised erythematous dermatitis which occurred for the first time responded well to therapy within 10 days. These cases were hospitalised and received adjuvant local non-specific therapy, which may also have been a contributory helpful factor to be considered. Of the 2 other cases of chronic nature 1 case showed a fair response and the other a poor response inspite of continuing therapy for 15 days.

Atopic Dermatitis: These cases of constitutional allergy are generally of a recalcitrant type. Two cases which were hospitalized were treated for 10 days with minimal improvement and the drug was discontinued as both the patients developed asthmatic complications.

Contact Dermatitis: One case due to an acriflavine dye sensitivity, following a post-operative application, responded well within a week, the other case a kum-kum sensitivity on the forehead in a woman who developed an erythematous infiltrated wheal-like lesion on the forehead responded in like fashion.

Prurigo: Four cases in children were given 2 mg, T. D. S. for a week and stepped up to 2 mg. Q. D. S. for a further period of week showed a fair response in 2 children, and a poor response in another 2.

Drug eruption: Two cases were due to sulpha sensitivity, 2 cases of penicillin sensitivity and 1 case of reaction due to meprobamate taken orally. All these cases developed severe urticarial lesions and angioneurotic oedema associated with severe pruritus. The response both subjectively and objectively was evident in 24 hours, total subsidence of lesions in 4 to 6 day's time.

Infectious Eczematoid Dermatitis: Two cases both had an initial eczematous patch on the dorsum of the foot, which after applying some irritant ointment, together with secondary infection, developed generalised allergic reactions on the body. The secondary lesions responded well and settled down with treatment and subsequently the primary patch was appropriately treated.

Henoch-Schonlein syndrome: Three cases presenting the classical triad of abdominal discomfort, joint pains and purpuric lesions on the skin were encountered. Two cases were brothers, with a prior history of sore throat. No drugs were administered and fresh purpuric lesions cropped up at intervals of 2 to 3 days. Investigations showed a mild leucocytosis, presence of erythrocytes in the stool examination, the platelet count, bleeding and coagulation time were within the range of normality. They were treated with cyproheptadine 2 mgm. Q. D. S. and within a week, fresh lesions stopped appearing and the older lesions showed subsidence in 18, 22 and 26 days of treatment, joint manifestations subsided in a fortnight's time. No recurrence of lesions were seen for a period of 4 months. The allergens responsible for this syndrome are dietetic or bacterial toxins; these allergens act by combining with the capillary endothelium which, when acted upon by the antibodies, is damaged, thus producing the various haemorrhagic exudative phenomena. The antihistaminic and antiserotonin effect of cyproheptadine at the capillary endothelial site helped in controlling the haemorrhagic exudative reaction. It can be seen, that in general, the acute exudative and dermal reactions responded better to therapy than ahe chronic and less exudative types.

Antipruritic Effect: In assessing this effect, besides the above mentioned cases, others with severe, persistent pruritus of diverse aetiology were included. The mechanism of pruritus in these diverse aetiological diseases cannot be identical, hence it was interesting to assess the results with this drug in these skin conditions. The results were assessed subjectively which are likely to have personal variations. However, confirmatory, objective observation can be made by finding out if the patients were comfortable or not, and by the appearance of the lesions. The result was assessed good if there was complete relief, fair if partial relief was obtained, and poor if there was no relief. Table II shows the results, including the previous group of cases tabulated before.

TABLE II

	Diseases	Good	Fair	Poor	Total
1.	Acute Urticaria ...	12	–	–	12
2.	Angioneurotic oedema ...	5	–	–	5
3.	Allergic dermatitis ...	3	1	1	5
4.	Atopic dermatits	–	–	2	2
5.	Contact dermatitis	2	–	–	2
6.	Prurigo	–	2	2	4
7.	Drug eruption	5	–	–	5
8.	Infectious eczematoid dermatitis	2	–	–	2
9.	Acute Generalised Lichen Planus	–	–	2	2
10.	Diabetic pruritus	–	–	2	2
11.	Pityriasis rosea	–	2	–	2
12.	Dermatitis herpetiformis ...	–	1	1	2
13.	Acute pruritic generalised psoriasis	–	1	1	2
14.	Toxic exfoliative dermatitis ...	–	–	1	1
		29	7	12	48

The results show that this drug has a good antipruritic effect in skin diseases of an allergic diathesis. Symptomatically, it is a valuable agent in other pruritic dermatoses, although it may not completely relieve them.

Toxic effects: This was noticed in 4 patients, the main complaint being drowsiness, which subsided on reducing the daily dose from 12 mgm. to 8 mgm. per day. One patient complained of intense thirst, the tablets were then advised to be taken with a glassful of water with sudsidence of the symptom. No significant disturbance in the leucocytic count was noticed in cases where the drug was administered for a long duration.

CONCLUSION

1. A new antihistamine, antiserotonin and antipruritic agent was used orally for a clinical trial in 51 cases.

2. The dual antagonistic action to histamine and serotonin make this drug a valuable agent, with a broader spectrum of activity than most conventional antihistaminic drugs, and this was evident in allergic cutaneous diseases, where the anti-allergic and antiexudative reactions were rapidly brought under control, though this effect was not appreciable in chronic prurigo–like lesions.

3. Three cases of Henoch–Schonlein Syndrome, responded well to therapy, with subsidence of skin lesions and joint manifestations. No recurrence of lesions were seen for a period of 4 months.

4. Although this drug is not a phenothiazine derivative, the antipruritic action was good and more pronounced in cutaneous diseases associated with allergic causative mechanism. The antipruritic effect of cyprohepatadine is probably related to its beneficial effect on the disease process rather than to primary senesory action.

5. Toxic effects and side reactions were comparatively minimal, no disturbance in the leucocytic count was noticed in the dosage in which the drug was used.

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