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BROCRESINE, A HISTIDINE DECARBOXYLASE INHIBITOR, IN CHRONIC URTICARIA*

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ABSTRACT

The histidine decarboxylase inhibitor brocresine, in doses from 600 mg to 1800 mg daily, failed to diminish skin histamine and histamine excretion in patients with chronic urticaria. A slight decrease in clinical symptoms was found, these data, however, are comparable to those found, when chronic urticaria patients are treated with placebo. No patient was cured after two weeks of treatment. Possible explanations of the lack of potent inhibition and discrepancies with observations of other workers are discussed.

Recent experiments by Levine (1) have aroused renewed interest in the inhibition of histamine biosynthesis in man. In mammalian tissues histamine is produced by decarboxylation of histidine. Mammalian histidine decarboxylases are of two main types. One type acts not only on histidine, but also on other aromatic amino acids, and is named non-specific aromatic L-amino acid decarboxylase. The second type which occurs in mast cells (2), certain tumors (3), and other rapidly growing tissues (4) is a specific enzyme acting only on histidine. Brocresine or NSD 1055, which is a 4-bromo-3-hydroxybenzyloxyamine-dihydrogen phosphate has been reported to be an inhibitor of both types of histidine decarboxylases (1, 5, 6, 7).

This paper reports on analyses of urinary and skin histamine in chronic urticaria before and during treatment with brocresine. The possible clinical effect of brocresine was also studied.

MATERIAL AND METHODS

The study included six men and ten women suffering from chronic urticaria. All patients had symptoms for more than three months. Before treatment, a general medical examination was performed and found to be normal. The laboratory examination included hemoglobin, leukocyte and differential counts, eosinophil and platelet counts, serum glutamic pyruvic transaminases (SGPT), serum creatine, potassium, sodium, chloride and Co_2, as well as urinalysis. All examinations were repeated after termination of the study. The urine was analysed weekly for protein and sugar. Leukocytes, platelets, and SGPT were also examined weekly. The blood pressure was measured daily through two weeks as well as after termination of the study. Two patients received treatment through fourteen weeks and two other patients through ten weeks. In one patient the study was discontinued after one week. The remaining eleven patients were treated for two weeks.

Brocresine† was given orally in three or four daily doses. The patients received from 600 mg to 1800 mg daily (10–30 mg per kg). In eleven patients, urinary histamine was measured before treatment and on the seventh, eighth, thirteenth and fourteenth day of treatment. Two patients had their urinary histamine measured after two months of treatment and two other patients after three months of treatment. Skin histamine was investigated in twelve patients before and after two weeks of treatment. The patients treated through ten or fourteen weeks had further analyses before the termination of treatment. All specimens were from grossly normal non-wealing skin. Histamine was determined spectrofluorometrically (8, 9).

The clinical response was evaluated in all patients by giving daily scores through two weeks for severity of disease and severity of itch. Scores for grading were 0 = none, 1 = mild, 2 = moderate and 3 = severe. Possible side-effects were registered simultaneously.

RESULTS

Figure 1 displays results of the first two weeks of clinical investigation. Within the first week of study, a moderate decline in total score for severity of disease and for itch could be demonstrated. During the following week the total scores remained almost constant. The clinical condition was improved in six patients after two weeks of treatment and in three of the four patients, who continued therapy for

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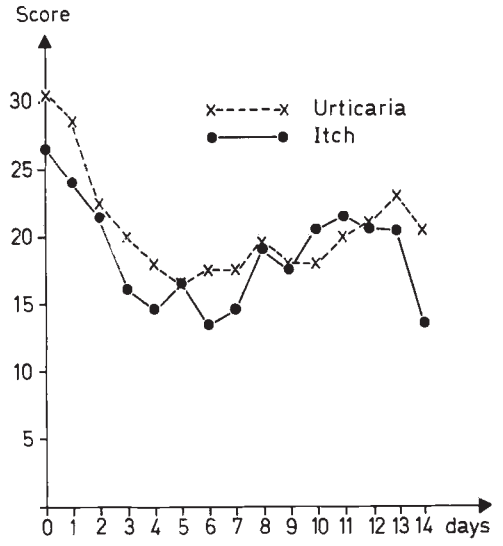

FIG. 1. Total score for urticaria and itch in 15 patients with chronic urticaria during two weeks of treatment with brocresine, 600–1800 mg per day. Individual scores for grading were 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

TABLE I

Mean urinary histamine per 24 hours in 10 patients with chronic urticaria, before and during first two weeks of treatment with brocresine, 600–1800 mg daily. One patient with excessive histamine excretion excluded

Day of treatment	Urinary histamine ± S.E. (μg/24 hr.)
−2	57 ± 5
−1	53 ± 6
7	58 ± 15
8	44 ± 6
13	47 ± 3
14	46 ± 4

ten or fourteen weeks. In one patient, treated through fourteen weeks, urticaria was completely unchanged.

Brocresine failed to diminish histamine excretion significantly (Table I). One patient with a very severe urticaria and angioneurotic edema displayed greatly increased urinary histamine values (1619 μg/24 h) before therapy and more moderately increased values (736 and 485 μg/24 h) after thirteen and fourteen days of treatment. When this patient was excluded, the mean urinary histamine was found within normal levels (15–90 μg/24 h) (8). Histamine excretion after ten or fourteen weeks of treatment is visualized on Table II.

No significant decrease of histamine could be found in non-wealing, grossly normal skin, either after two weeks of treatment (Table III)

TABLE II

Urinary histamine per 24 hours in 4 patients with chronic urticaria before and during ten or fourteen weeks of treatment with brocresine, 1200–1800 mg daily

Sex/ Age	Dosage (mg/day)	Urinary histamine (μg/24 hr.)				
		Before treatment	After 1 week	After 2 weeks	After 10 weeks	After 14 weeks
M/52	1800	80	53	44	65	
		81	31	40	50	
F/40	1800	46	15	55	36	
		24	17	55	55	
F/37	1800	32	30	52		34
		39	37	52		25
F/26	1200	41	178	44		32
		32	31	40		27

TABLE III

Skin histamine levels in grossly normal dried and defatted thigh skin of 12 patients with chronic urticaria before and after two weeks' treatment with brocresine

Sex/Age	Dosage (mg/day)	Skin histamine (μg/g)	
		Before treatment	After treatment
M/68	600	19.4	16.4
F/56	600	21.2	19.9
F/33	600	17.8	15.6
M/43	1200	44.6	22.0
F/26	1200*	21.5	18.2
M/41	1200	13.4	10.8
F/26	1200	14.1	16.4
M/44	1600	18.4	20.2
F/69	1200	27.1	19.8
F/37	1800	29.7	28.1
F/36	1200*	27.1	27.2
F/24	1200	29.8	32.6
Mean ± S.E.		23.7 ± 2.5	20.6 ± 1.8

* During second week of treatment 1600 mg brocresine per day.

TABLE IV

Skin histamine levels in grossly normal dried and defatted thigh skin of 4 patients with chronic urticaria before and after ten or fourteen weeks of treatment with brocresine, 1200–1800 mg per day

Sex/Age	Dosage (mg/day)	Duration of treatment (weeks)	Skin histamine (μg/g)	
			Before treatment	After treatment
M/52	1800	10	32.0	42.1
F/40	1800	10	34.6	35.9
F/37	1800	14	29.7	32.6
F/26	1200	14	17.4	33.4

or after treatment for ten or fourteen weeks (Table IV).

In one patient, treatment was discontinued after one week due to a slightly elevated SGPT, which rose from 0.5 units per ml to 2.3 units per ml. After cessation of therapy, the values returned to normal within a week. No other side effects were demonstrated by laboratory examination. Subjective side effects were mild sedation and weariness in one patient and headache in another patient. This patient, however, admitted having frequent headaches prior to treatment.

DISCUSSION

The clinical data presented are comparable to those found when chronic urticaria patients are treated with placebo (10). None of our patients were cured after two weeks of treatment.

The results of this study contrast with those of Levine (1), who studied the effect of brocresine on two men without any abnormality in histamine metabolism and on two women with extensive systemic mastocytosis. Inhibited biosynthesis of histamine was demonstrated in all four subjects. The studies, however, are not comparable, because Levine used histidine loading. Our data agree with the findings of Demis (11), who failed to diminish histamine excretion by brocresine in patients with systemic mast cell disease. In studies on rats Johnston and Kahlson (12) found that a single injection of brocresine gave a 54 per cent inhibition of histamine formation when this was judged by the output of isotopic histamine after injection of 14 C histidine. However, only repeated injections of brocresine gave a moderate degree of inhibition when a non-isotopic method was employed. They proposed that, for unknown reasons, brocresine interferes more readily with conversion of injected histidine than with the substrate normally contained in the cells. This may account for the negative results of the present study. Our data on skin histamine confirm the lack of potent inhibition of histamine formation by brocresine in man. The data on skin histamine are in accordance with studies by Green and Erickson (13), who found no significant change in rat heart histamine concentration after brocresine. Our study has shown no clear evidence of toxicity and a notable absence of side effects in most cases.

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