

Treatment of chronic idiopathic urticaria with combined H1 and H2 blockers

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Summary

Combined H1 (cyproheptadine) and H2 antihistamines (cimetidine) were tried in eight patients with chronic urticaria who were previously unresponsive to conventional anti-urticarial regimens, including type I antihistamines, hydroxyzine, ephedrine and corticosteroids. 50% of the patients responded with 90% or greater improvement within 10 days. The remaining 50% showed no benefit. Side effects of the medications were minimal. These results indicate that a 10 day trial of both H1 and H2 antihistamines may be useful in patients with chronic urticaria resistant to all other standard treatment modalities.

Introduction

Chronic urticaria is a common disease; yet it is frequently an uncomfortable problem for both the physician and the patient. In most studies (Green, Koelsche & Kierland, 1965; Champion *et al.*, 1969), a specific cause of the urticaria is found in less than 30% of the patients. The physician must therefore treat the patient symptomatically. The mainstay of therapy has been the H1 antihistamines: hydroxyzine, ephedrine and corticosteroids, in various combinations (Sheldon, Lovell & Mathews, 1967; Fink, 1972). A significant number of patients are unresponsive to all these modalities. Although other mediators besides histamine may be involved, it is possible that such therapeutic unresponsiveness is due to the presence of type II histamine receptors in dermal vessels, which are not blocked by the type I antihistamines (Black *et al.*, 1972). This is supported by studies demonstrating only partial inhibition of histamine-induced pruritis and weal and flare by type I antihistamines (Galant *et al.*, 1973; Cook *et al.*, 1973), and elimination of histamine-induced weals by a combination of H1 and H2 blockers (Black *et al.*, 1972; Hutchcroft, Moore & Orange, 1978). With the recent availability of the type II antihistamine, cimetidine (Haggie, Fermont & Wyllie, 1976;

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Blackwood *et al.*, 1976), we decided to initiate a pilot study to evaluate the effect of treatment with cimetidine alone or in combination with a type I antihistamine in patients with refractory chronic urticaria. A 50% success rate of this regimen in eight patients forms the basis for this initial communication.

Materials and methods

Eight patients with chronic refractory urticaria were studied. Chronic urticaria was defined as any urticarial episode lasting 6 weeks or longer (Warin & Champion, 1974).

Most of these patients were referred by the practicing allergists, after unrewarding extensive evaluation, to the Clinical Immunology Division and Vasculitis Study Group at the University of Colorado Medical Center (Phanuphak, Claman & Kohler, 1977). All patients failed to respond to regimens including type I antihistamines, hydroxyzine, ephedrine, terbutaline and in several cases corticosteroids. As part of the evaluation, many of the patients underwent skin biopsies, extensive blood studies and serum or plasma histamine determinations. Age, sex, duration of disease, skin biopsy results and previous medications are shown in Table 1.

Table 1. History of eight chronic urticaria patients treated with combined H1 and H2 antihistamines

Patient	Age (years)	Sex	Duration of urticaria*	Histopathology of urticaria	Previously failed therapies†
D.M.	59	F	6 M	Perivasculitis	C+E, D, Hy, P
S.D.	35	F	1.5 Y	Acute vasculitis	C+E, H1, Hy, P
C.C.	37	F	4 M	Perivasculitis	C+E, H1, Hy
W.Y.	40	M	10 M	Acute vasculitis	C+E, D, Hy, P
L.G.	34	F	14 Y	Perivasculitis	H1, Hy, P
D.G.	50	F	4 M	Perivasculitis	C+E, Hy
B.H.	63	F	3 M	n.d.	D, H1, Hy, P
H.M.	63	F	12 Y	n.d.	D, H1, Hy, P

n.d. = Not done.

* M = Months; Y = years.

† C = Cyproheptadine (Periactin®); D = diet manipulation; E = ephedrine or epinephrine; H1 = H1 antihistamines; Hy = hydroxyzine (Atarax®); P = prednisolone or ACTH.

Seven patients were treated with cimetidine, 300 mg q.i.d., and cyproheptadine, 4.0 mg q.i.d., for 7–10 days. One patient was treated with cimetidine alone. If no improvement occurred within this period the medications were withdrawn. In those patients who responded, the regimen was continued from 3 weeks to 2.5 months. Following this, medications were gradually withdrawn one at a time, and the patient response was observed.

Response to therapy was determined by the patient's own estimation of improvement of symptoms (reduction of itching), the absence of recurrence and the observation of the disappearance of the skin lesions by the patient and the evaluating physician. Prior to the initiation of this therapeutic trial, the therapeutic rationale and possible side effects of the regimen (Sharpe & Hawkins, 1977) and the experimental nature of the study were explained to each patient.

Table 2. Treatment results of eight chronic urticaria patients with combined cyproheptadine and cimetidine

Patients	Duration of treatment (weeks)	Results	Status after stopping treatment
D.M.	12	100% improvement	Remission for 3 weeks now*
S.D.	1.5	No improvement	—
C.C.	4	No improvement	—
W.Y.	6	100% improvement	Remission for 3 weeks now
L.G.	1	No improvement	—
D.G.	1.5	No improvement	—
B.H.	3	90% improvement	Remission for 3 weeks now
H.M.†	3	100% improvement	Continues on cimetidine

* Follow-up up to January 12, 1978.

† On cimetidine alone without cyproheptadine.

Results

The results of the treatment are shown in Table 2. Four out of eight patients had 90 to 100% improvement, as previously defined. The remaining patients had no improvement after the 7–10 day trial. In all responders, improvement was observed within 4 to 5 days and maximum benefit was seen in 7 to 10 days. The improvement was sustained during the time that the drugs were continued. In all four responders, there was no recurrence of symptoms for a minimum of 2–4 weeks so far, following withdrawal of both drugs. In patient D. M., during the first round of her withdrawal, she broke out with hives on cimetidine alone following withdrawal of cyproheptadine, but the symptoms were rapidly brought under control when cyproheptadine was resumed. A second round of withdrawal has not resulted in recurrence so far.

Discussion

In the group of eight patients with refractory chronic urticaria studied, the use of the combination of an H1 antihistamine (cyproheptadine) and an H2 antihistamine (cimetidine) resulted in the resolution of urticaria in 50% of patients, which was sustained after the discontinuation of medication. Although this was only a pilot study and not blind, each patient served as his or her own control, having suffered from urticaria despite conventional therapy for a period of at least several months. In addition, no major side effects were noted from the regimens, other than the occasional drowsiness and increased appetite seen with cyproheptadine.

In addition to the therapeutic implications of this study, the results support the presence of H2 receptors in the involved skin vessels of some individuals (Black *et al.*, 1972). This may provide an explanation for the incomplete inhibition by H1 antihistamines of histamine-induced weal and flare reactions (Galant *et al.*, 1973; Cook *et al.*, 1973). The combination of H1 and H2 blockers has also been demonstrated to be effective in animals in blocking the local dermal oedema produced by histamine (Black *et al.*, 1972; Hutchcroft *et al.*, 1978). One potential problem, however, in the use of an H2 antihistamine is the inhibition of the negative feedback histamine exerts on mediators released by the mast cells (Lichtenstein & Gillespie, 1973). It has been demonstrated that histamine stimulates adenyl cyclase via an H2 receptor, leading to an increase in intracellular cyclic AMP (Bourne *et al.*, 1974). This response to

histamine is inhibited by the H₂ blocker (Lichtenstein & Gillespie, 1973; Beaven, 1976), and might potentially raise circulating histamine levels. In light of this possibility we added an H₁ antihistamine to hopefully block all receptors and counteract the effect of the extra histamine. The choice of cyproheptadine may have provided inadequate H₁ blockade in the four patients who did not respond, since some evidence suggests this drug may be a weak H₁ histamine blocker (Rhoades *et al.*, 1975). In the future we plan to use hydroxyzine as a more potent H₁ blocker.

In conclusion, considering the increasing experience with the use of cimetidine in peptic ulcer disease and its relative lack of side effects (Sharpe & Hawkins, 1977), in addition to the demonstration of its possible efficacy in refractory urticaria, we believe that further study of the efficacy of H₂ antihistamines in allergic disease is indicated.

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Note added in proof

We have treated six additional patients with chronic urticaria unresponsive to therapy. Upon addition of cimetidine to hydroxyzine, two did not respond and four have had complete remission.

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