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Efficacy of Cetirizine in Cholinergic Urticaria

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In order to examine the efficacy of cetirizine in cholinergic urticaria, we studied 24 patients in a double-blind crossover design during 3-week treatment periods, with either 10 or 20 mg/d cetirizine or placebo. The placebo period was always placed in between the two verum treatments to allow for a washout of the drug. Evaluation of the patients' daily symptom scores based on itching, erythema and whealing showed a highly significant improvement ($p < 0.01$). The percentage of days with mild or no symptoms was also increased significantly with the drug ($p < 0.05$). Except for whealing ($p < 0.05$), no significant differences between the two dosages of cetirizine could be determined. Since antihistamines have previously been shown to be frequently unsatisfactory in the treatment of cholinergic urticaria, the present data are encouraging regarding the control of symptoms in this condition. ***Key word: antihistamine.***

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Cholinergic urticaria is a disease that afflicts more than 10% of young adults at varying severity (1). Whealing is provoked by physical exercise, passive overheating and mental stress. Symptoms are induced by mediator release from mast cells and basophils and range from mild pinpoint whealing and itching to severe systemic reactions (1–5).

In contrast to other types of urticaria, which respond readily to antihistamines, treatment of cholinergic urticaria remains a problem. Thus, in a previous study with the H1-antagonist ketotifen, we have shown a 95.8% response rate in dermographic urticaria and only a 69.2% responsiveness in cholinergic urticaria (6). In another study of 4 patients with cholinergic urticaria who were unresponsive to conventional antihistamines, McClean et al. (7) noted improvement in 3 patients by treating them with up to 8 mg/d ketotifen (ordinarily 2 mg/d), a dose that is known to be associated with considerable adverse events (8). There is thus a need for a more effective treatment of cholinergic urticaria.

Cetirizine is a new non-sedative antihistamine that has been shown to be a potent H1-antagonist with additional antiallergic effects, such as inhibition of eosinophil infiltration, which is known to occur in cholinergic urticaria (9–12). We have therefore decided to study this drug for its efficacy in cholinergic urticaria at its recommended daily dose of 10 mg as well as at twice that dose. A double-blind crossover, within-patient comparison against placebo was chosen, since the severity of symptoms in this disease is highly variable from patient to patient.

METHODS

Four dermatology clinics participated in the study. Eligible patients had been suffering from cholinergic urticaria for at least 1 month, and their disease had to be verified by the provocation tests commonly used for the diagnosis in each specific clinic, such as physical exercise. Exclusion criteria were ages < 18 and > 65 years, pregnancy, lactation and liver, cardiac or renal dysfunctions. Patients had to be off the following drugs for at least the given number of days: astemizole 60, ketotifen 15, corticosteroids 7, common H1-antagonists 4 and anticholinergics, β-sympathomimetics and β-blockers 2 days each.

Patient history included duration of cholinergic urticaria, triggering factors, usual symptoms, frequency of attacks and previous treatments as well as their efficacy.

After informed consent, patients were treated in a double-blind, randomized fashion for 3 weeks with either cetirizine 10 or 20 mg/d, followed by a 3-week period on placebo (single-blind) and another 3-week treatment period with the remaining cetirizine dose. Patients were asked to keep a daily record of their symptoms using a diary card and a score of 4 regarding pruritus, erythema and whealing (0 = absent, 1 = mild, 2 = moderate, 3 = severe). Space was also provided to make remarks about eliciting factors on a daily basis. At the beginning of the trial, 1 week after start of treatment and at the end of each treatment and the in between placebo period, the patient was evaluated by the physician regarding global efficacy on a visual analogue scale and regarding symptoms after provocation with the 4-point symptom score noted above. At each visit, histamine prick tests were done to check for compliance, and patients were questioned regarding their general well-being and whether they had observed anything unusual regarding their health.

Data from the diary cards and the case record forms were evaluated using the Friedman two-way analysis of variance by ranks.

RESULTS

From the four clinics participating, a total of 25 patients were entered (12 from Berlin, UKRV, 3 from Berlin, Charité, 9 from Vienna, 1 from Leipzig). Twenty-four patients, 14 females and 10 males, were available for final analysis. One patient had to be excluded because of major protocol violation (wrong inclusion criteria).

Basic data on all patients and their disease are shown in Table I. Patients were mostly young adults who had suffered from the disease from 0.08 to 25 yrs. As evident from their symptom scores at the start of the trial, they all suffered from mild to moderately severe itching and moderate erythema and whealing.

Table I. *Basic data (means ± SD) on the 24 evaluable patients*

Age (years)	26.06 ± 7.30
Disease duration (years)	5.12 ± 6.21
Baseline symptom score	
whealing	1.96 ± 0.95
erythema	1.96 ± 0.95
pruritus	2.12 ± 0.80

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Table II. *Triggering factors of cholinergic whealing, as mentioned by the patient at study entry*

Triggering factors	Number of patients
Exercise/sports	23
Emotions/stress	12
Warm temperature/clothes	11
Shower/bath	3
Sweating	2

Two patients suffered also either from periorbital edema or dizziness, shortness of breath and vomiting during attacks. Triggering factors for cholinergic urticaria bouts were mostly exercise, followed by emotional factors and warmth due to increased ambient temperature or clothes (Table II). Most patients ($n = 16$) had received other antihistamines, with unsatisfying results in almost all cases (Table III). Two patients had even received corticosteroids, with moderate and bad results, respectively.

Evaluation of the patients' diary cards yielded highly significant results on overall comparison for all parameters except erythema ($p = 0.008$ for pruritus, $p = 0.01$ for whealing). Differences between the two cetirizine doses were significant only for whealing ($p = 0.04$). The percentages of days with no or only mild symptoms were 57 ± 35 on placebo, 74 ± 27 on 10 mg/d and 81 ± 17 on 20 mg/d cetirizine (overall significance: $p = 0.02$; comparison 20 mg/d vs placebo: $p = 0.01$).

Evaluation of the data from provocation tests proved to be an impractical approach, as the symptoms without drug showed a high intraindividual variation between tests before study and at the end of the placebo period, making further comparison impossible. This lack of reproducibility of cholinergic urticaria on exercise provocation has been described before (13).

Treatment was generally well tolerated by all patients (Table IV). One patient suffered from diarrhea during the first week on 10 mg cetirizine, but the symptoms then resolved spontaneously. One patient noted mild, transient loss of appetite at the same dosage during the first treatment week only. Another observed mild tiredness at the 10 mg/d, but not at the 20 mg/d dose. Two subjects experienced moderate or mild, continuous tiredness at the 20, but not at the 10 mg/d dose. One patient asked for a change of treatment while on placebo because of severe symptoms.

Table III. *Anamnestic data on the benefit of diverse H1-antagonists in the patient population studied*

H1-antagonist	Response		
	Good	Medium	Bad
Terfenadine (120 mg/d)	0	1	6
Astemizole	1	4	2
Pheniramine	0	1	1
Oxatomide	0	0	1
Ketotifen	0	0	1
Clemastine	1	3	0
Hydroxyzine	0	1	0
Mebhydroline	1	1	0
Loratadine	1	1	0
Cetirizine	3	1	0
All agents	6	14	11

Table IV. *Adverse events noted by the patients*

Symptoms	Treatment period		
	10 mg	20 mg	Placebo
Diarrhea	1	0	0
Loss of appetite	1	0	0
Tiredness	1	2	0

DISCUSSION

The present study involved a patient group typical of cholinergic urticaria in that most patients were young adults who could provoke their bouts of whealing after vigorous exercise and whose symptom scores were moderate to severe (Tables I–II). The patients' history also exhibited the previously noted treatment refractoriness with conventional sedative antihistamines (6, 7), with the exception of mebhydroline. Better results were obtained with nonsedative antihistamines (Table III). Based on the several evaluation criteria employed, cetirizine was highly effective at both doses studied regarding clinical symptoms. The drug was furthermore well tolerated even at its higher dose (Table IV), making it a highly effective, albeit only symptomatic treatment of the disease. The efficacy of cetirizine is underlined by the highly satisfying results noted by patients who were treated with the drug prior to entering the present study (Table III).

The design of the present study posed some problems at the time of planning because the disease is known to be highly variable from patient to patient and because symptoms are provoked by the patient in dependence of his physical activity, ambient temperature and mental stress factors (1, 2). Making use of a diary card proved to be a good approach for the assessment of disease activity. Evaluation of the symptoms after exercise provocation by the physician was on the other hand, less convincing. This lack of sensitivity of an apparently objective assessment is probably due to the well-known fact that exercise provocation is reproducible in only 64% of patients (13). Reasons may be an insufficient rise in the core temperature during testing or patient refractoriness, which is noted by many patients for a variable length of time after provocation of their symptoms (2). Thus, for diseases that have a variable symptomatology depending on daily activity and that cannot be reproduced consistently, daily symptom scores seem to be the most reliable method for evaluation of the efficacy of a drug.

Of the many types of urticaria known, dermographic and cholinergic urticaria are both characterized by a fleeting wheal lasting generally less than 1 h (2). One would expect both to have similar mediators involved and to respond equally well to H1-antagonists. This is clearly not the case for agents that have been compared directly in the two conditions (6). The potential involvement of additional mediators apart from histamine in

cholinergic urticaria, such as serotonin and eosinophil chemotactic agents, as shown before (4, 5), is indicated by the demonstration of eosinophils and their products in lesions biopsied 10 min after provocation, but not in control skin of patients (12). The high efficacy of cetirizine in cholinergic urticaria, as shown here, can perhaps be explained by the potent anti-chemotactic activities for eosinophils, as noted before both in vivo and in vitro (10, 11).

Nevertheless, symptoms are not totally suppressed by cetirizine, and larger studies testing higher doses of this or other drugs in this condition are thus necessary to identify methods for a better control of symptoms and the basic pathology of the disease.

REFERENCES

1. Zuberbier T, Althaus C, Chantraine-Hess S, Czarnetzki BM. Prevalence of cholinergic urticaria in young adults. J Am Acad Dermatol, in press.
2. Czarnetzki BM. Urticaria. Berlin: Springer, 1986.
3. Herxheimer A. The nervous pathway mediating cholinergic urticaria. J Clin Science 1956; 15: 195–204.
4. Kaplan AP, Beaven MA. In vivo studies of the pathogenesis of cold urticaria, cholinergic urticaria and vibration-induced swelling. J Invest Dermatol 1976; 67: 327–332.
5. Soter HA, Wassermann SI, Austen KF, McFadden ER. Release of mast cell mediators and alterations in lung functions in patients with cholinergic urticaria. N Engl J Med 1980; 302: 604–608.
6. Cap J-P, Schwanitz HJ, Czarnetzki BM. Die Wirkung von Ketotifen bei der Urticaria factitia und der Urticaria cholinergica im gekreuzten Doppelblindversuch. Hautarzt 1985; 36: 509–511.
7. McClean SP, Arreaza EE, Lett-Brown MA, Grant JA. Refractory cholinergic urticaria successfully treated with ketotifen. J Allergy Clin Immunol 1989; 83: 738–741.
8. Czarnetzki BM. Ketotifen in cholinergic urticaria. J Allergy Clin Immunol 1990; 86: 138–139.
9. Campoli-Richards DM, Buckley MM, Fitton A. Cetirizine. A review of its pharmacological properties and clinical potential in allergic rhinitis, pollen-induced asthma, and chronic urticaria. Drugs 1990; 40: 762–781.
10. Charlesworth EN, Kagay-Sobotka A, Norman PS, Lichtenstein LM. Effect of cetirizine on mast cell-mediator release and cellular traffic during cutaneous late-phase reaction. J Allergy Clin Immunol 1989; 83: 905–912.
11. Fadel R, Herpin-Richard N, Rihoux JP, Henocq E. Inhibitory effect of cetirizine 2HCl on eosinophil migration in vivo. Clin Allergy 1987; 17: 373–379.
12. Haas N, Motel K, Czarnetzki BM. Comparative immunoreactivity of eosinophil constituents in different types of urticaria. Arch Dermatol Res, in press.
13. Hirschmann JV, Lawlor F, English JSC, Louback JB, Winkelman RK, Greaves MW. Cholinergic urticaria. Arch Dermatol 1987; 123: 462–467.