Effect of Cetirizine on Cutaneous Reactions to PAF, Kallikrein and Serum in Patients with Chronic Urticaria

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The effects of oral administration of the antihistamine cetirizine on the weal and flare caused by intradermal injection of platelet activating factor (PAF-acether), kallikrein, histamine and the patient's own serum were investigated in 10 patients with chronic urticaria. Cetirizine markedly reduced the weal and flare induced by all these agents as measured 12 min after the injections. The delayed reactions observed after injection of PAF, kallikrein and serum were also inhibited by cetirizine at 6 hours. In addition, reactions which were present 20 h after injection of the agent before administration of cetirizine were found to be inhibited at the same point in time after cetirizine treatment. These effects might explain the good inhibitory clinical effect of cetirizine on the patients' urticaria. No side-effects were noted during the treatment.

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Patients with chronic urticaria sometimes show increased and delayed reactions to intracutaneous injection of their own (autologous) serum as well as to inflammatory mediators such as kallikrein (1, 2). Intracutaneous injection of synthetic platelet activating factor (PAF-acether) is known to induce a weal and flare in normal subjects, but its effects in patients with chronic urticaria are not known (3, 4). Cetirizine is an effective antihistamine which has been used in patients with chronic urticaria with no or minimal sedative side-effects (5). It is mainly known for its antihistaminic actions and has very weak affinity in vitro for α-adrenoreceptors and muscarinic receptors (6). Observations in pollen-sensitive patients indicate, however, that it might inhibit the release of PAF in inflammatory reactions and block the PAF-induced appearance of eosinophils (7, 8).

In the present study the effects of the above-mentioned inflammatory mediators were investigated in patients with chronic urticaria before and during treatment with cetirizine.

METHODS

Procedure

The first intracutaneous test was usually performed at noon on Mondays. The weal and flare were outlined on transparent plastic foil at 0.2, 6 and 20 hours and measured planimetrically. The patient was given one 10 mg tablet of cetirizine after the 20-hour reading and then at 7 pm and 7 am for 3 days. The intracutaneous test was repeated at noon on Wednesday. The effects of the treatment and any side-effects were noted.

Agents used for tests

PAF-acether (Sigma, St Louis, MO, US) 100 µg in 0.02 ml. It was dissolved immediately before use in PBS solution containing 0.025% human serum albumin. *Kallikrein* (Padutin® Bayer AG, Leverkusen, Germany): To 40 U of the dry powder 1 ml of saline was added and 0.02 ml was injected. *Histamine:* coated prick needles (Phazet Pharmacia, Uppsala, Sweden) were used.

Serum

Blood was drawn before the first test and the serum was separated by centrifugation. It was kept cold until used. *Saline* was used as a control.

Table I. *Mean weal and erythemal area in mm² ± SD 0.2, 6 and 20 hours after intradermal injection of PAF, kallikrein, autologous serum and histamine prick test in 10 patients with chronic urticaria. Tests were performed before and after treatment with cetirizine 10 mg × 2 for 3 days. D: Mean percentage difference for each patient before and after cetirizine. ***p<0.001, **p<0.01, *p<0.05*

	Weal before cetirizine			Weal after cetirizine		
	0.2 h	6 h	20 h	0.2 h	6 h	20 h
PAF	296	1 282	257	110	229	8
	±86	±1 632	±452	±50	263	±26
				D −63**	−82***	−97**
Kallikrein	145	148	0	56	21	0
	±70	±177	–	±45	±26	–
				D −62**	−86***	–
Histamine	84	35	0	6	0	0
	±65	±84	–	±6	–	–
				D −93***	−100	–
Serum	96	128	31	26	12	0
	±51	±153	±73	±24	±20	–
				D −73**	−91*	−100
Saline	11	0	0	4	0	0
	±9	–	–	±3	–	–
	Erythema before cetirizine			Erythema after cetirizine		
PAF	1 915	680	14	350	30	0
	±710	±1 731	±43	±304	±51	–
				D −82***	−96*	–
Kallikrein	374	0	0	43	0	0
	±535	0	–	±69	–	–
				D −89		
Histamine	933	67	0	62	0	0
	±591	±148	–	±117	–	–
				D −93***	−100	
Serum	622	11	0	64	11	0
	±619	±34	–	±85	±33	–
				D −90**		

Patients

Ten patients, five men and five women aged 22–58 years, who had had chronic essential urticaria for more than 6 months, were tested on the wards. None of them had used any corticosteroids in the last month or taken any drugs in the last week. The tests were performed on the volar aspect of the forearm. The site of the injection varied from one patient to another, but the corresponding site on the other arm was used for retesting after cetirizine treatment.

Statistical analysis

For each agonist, the differences between the areas (weal and erythema) observed before and after cetirizine treatment were computed. A univariate analysis of variance was performed to test these differences (the null hypothesis is: There is, by condition, no difference between "before" and "after" cetirizine). The differences were globally compared by means of a multivariate analysis of variance for repeated measurements.

RESULTS

Injection of serum induced an immediate flare in seven of the patients, and this disappeared within 30 minutes. A weal which enlarged immediately after injection was seen in six patients. After 6 hours a weal was noted in seven patients and in two of them it

remained for 20 hours. The weal and flare in response to serum were markedly reduced by cetirizine, as were the reactions to PAF, kallikrein and histamine (Table I). The spontaneous urticaria improved or ceased to occur in all of the patients during cetirizine treatment. No drowsiness or other side-effects were noted.

DISCUSSION

In a study by Malmros (9) a weal and flare reaction to intradermal injection of the patient's own serum was observed in 5 per cent of 900 patients tested, mainly in those in whom an allergic aetiology was probable (9). In patients with chronic urticaria increased and delayed reactions have been reported (1, 2). The factor inducing the reaction is still unknown, but it is possible that histamine release plays some role. The maximal size of the weal at 6 hours is not consistent, however, with the idea of histamine release alone as the underlying factor.

PAF-induced weals in humans are not significantly reduced by the antihistamine chlorpheniramine (10). This might suggest that the strong inhibitory effect of cetirizine on the PAF-induced weals in the present study could be due to an anti-PAF effect of this drug. Nevertheless, it has been shown that cetirizine behaves differently from a PAF antagonist, since it is able to inhibit both PAF and FMLP eosinophil chemotaxis in vitro, whereas the PAF antagonist BN 52021 only inhibits chemotaxis induced by PAF (11).

Another antihistamine, ketotifen, has also been found to inhibit the PAF reaction, an effect which was thought to be due to its antihistaminic properties (12). An inhibition of the immediate PAF-induced flare by antihistamine (13) can be explained by nerve blockade, since anaesthetic properties are common to several antihistamines, but cetirizine seems to be devoid of any local anaesthetic effect in experimental animals (Dauby J, personal communication).

Kallikrein, which releases kinins, has been shown to cause increased delayed reactions in chronic urticaria (1). The fact that the reaction in the present study was less marked than in previous ones may have been partly due to the smaller volume injected. Since in recent years we have noted less strong positive delayed reactions in chronic urticaria even in tests with 0.1 ml of kallikrein, it is possible that an increased purification may have weakened its effect in the skin as a result of loss of stabilizers. However, cetirizine was also found to inhibit its effect markedly, an observation which has been made previously with antihistamines such as mepyramine and cyproheptadine in patients with chronic urticaria (13).

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