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Nimodipine versus terfenadine in the treatment of physical stimulus-induced urticaria

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Basophil and mastocyte degranulation is calcium-dependent. Calcium-antagonists can inhibit synthesis of and release *in vitro* some mediators in various types of cells. Both immunologically stimulated and non-immunologically stimulated release of material from basophils isolated from normal and allergic subjects can be antagonized by calcium blockers. The present study was aimed at testing the therapeutic effects and side effects of nimodipine therapy, a new dihydropyridine anti-calcium derivative for physical stimulus-induced urticaria, in comparison with a standard H_1-antihistamine therapy. The study was done in 32 outpatients who had physical stimulus-induced urticaria: 20 patients received nimodipine three times a day in a daily dose of 180 mg, 12 patients were treated with terfenadine in a dose of 120 mg. In the majority of patients treated with both nimodipine and terfenadine, satisfactory clinical results were obtained after 3 weeks of therapy. There were, however significant ($P < 0.05$) differences in responses. Complete clearance after 3 weeks was noted in 50% patients treated with nimodipine, whereas only 16% of patients on terfenadine were completely clear, and some showed only slight improvement. The treatment was easily manageable, and with few side effects.

Key words: calcium-antagonists; nimodipine; physical urticaria; terfenadine

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Basophil and mastocyte degranulation is a calcium-dependent event (5, 14). The mediators secreted by the mastocytes may derive from stores in the cell or synthesis *ex novo*. Each mediator contributes specifically to the allergic response and to the inflammatory phenomena (30). Calcium-antagonists have very complex effects on the degranulation of mediators in the mastocyte and basophil. They can inhibit synthesis of and release *in vitro* mediators such as histamine, PAF, leukotrienes and thromboxane A_2 in various types of cells (4, 19, 22, 24). Both immunologically and non-immunologically stimulated release of histamine from basophils isolated from normal and allergic subjects can be antagonized by verapamil, diltiazem and dihydropyridine, all dose-dependently (2, 25, 26). Since calcium inhibitors can antagonize basophil degranulation *in vitro*, it appeared worthwhile to evaluate the clinical effects of these drugs *in vivo* for treatment of skin diseases in which basophils and mastocytes are involved, such as urticaria, with a new dihydropyridine anti-calcium derivative called nimodipine (14). The present study was aimed at testing the therapeutic and side effects of nimodipine therapy for physical stimulus-induced urticaria in comparison with a standard H_1-antihistamine therapy.

MATERIAL AND METHODS

The study was conducted in 32 outpatients who had physical stimulus-induced urticaria that had been active for at least 3 months. There were 32 patients, 12 males and 20 female, aged 16 to 66 years (M 18–66; F 16–50). None of the subjects was taking other calcium-antagonists.

Table 1

Clinical response to nimodipine and terfenadine in different types of urticaria

	Demographic urt.		Solar urt.		Cholinergic urt		Acquired cold urt.	
	Nimod.	Terf.	Nimod.	Terf.	Nimod.	Terf.	Nimod.	Terf.
No improvement	-	2	-	1	2	-	2	-
Slight improvement	1	-	-	2	-	1	-	1
Marked improvement	3	-	-	-	2	2	-	1
Complete clearance	5	1	5	-	-	1	-	-

The patients were treated as follows: 20 patients received nimodipine three times a day in a daily dose of 180 mg. 12 patients were treated with terfenadine in a dose of 120 mg daily for 3–4 weeks. Blood pressures were taken at the start and end of treatment. We chose physical stimulus-induced urticarias for their extreme reproducibility (18), and the results of treatment were evaluated by stimulating our patients before and after therapy with suitable provocation tests. For cold urticaria we used the copper cup application test kept at 0°C on forearm skin (7), the arm immer in cold water, and if the subject did not show any typical response we placed him in a cold room at 4°C for 20 min (21). For all subjects with cold urticaria we excluded any secondary forms after assay of cryoglobulin, cryofibronogen and hemolysin in the cold. For cholinergic urticaria (6) we used intradermic injection of metacholine inducing an erythematic and whealing eruption with sweat. For solar urticaria (17) we phototested with a solar-simulated radiation (Oriel Corporation). The spectrum of emission is typical for a xenon lamp ranging from ultraviolet UVB to infrared radiation. Using specific filters the emission can be cut in UVB, UVB + UVA, UVA, visible light or solar-simulated radiation. When testing with total light, stimuli were 0.5–1 J/cm^2 whilst for UVB 10–70 mJ/cm^2 and for greater wave-length energy was 40 J/cm^2 (29). Dermographic urticarias were analysed by rubbing skin of the dorsal region with a blunted instrument: readings were taken after 12–20 min.

By this method we found 12 patients with dermographic urticaria, eight with solar urticaria, eight with cholinergic urticaria and eight with acquired cold urticaria.

The theraputic results were evaluated by the following scale:

1. complete clearance: complete disappearance of lesion after retesting;
2. marked improvement: moderate eruption of wheals with itching after retesting;
3. light improvement: decrease in size of wheals, but wheals always present;
4. no improvement: no change in the skin lesions from condition before treatment.

We also recorded any side effects that occurred during treatment.

RESULTS

Therapeutic results are shown in Table 1. In the majority of our patients, treatment with both nimodipine and terfenadine produced satisfactory clinical results after 3 weeks. Nimodipine appears to be better than terfenadine but in view of the heterogenicity of the physical urticaria we cannot make any statistical evaluation. Complete clearance after 3 weeks was noted in 50% patients treated with nimodipine, whereas 16% on terfenadine were completely cleared and some showed only slight improvement. The most successful results in the nimodipine-treated group were seen in the sun-sensitive patients. The subjects had not changed their usual habits of exposure to sun nor had they used any sun-screen preparations. These patients had had erythema and swelling in the phototest. When retested after 3 weeks of treatment all five patients had no reactions.

Since skin exposed to light or skin that has recently been affected by an acute episode might be refractory to the test, giving a false

negative (28), the gluteus muscles and the back were irradiated and both were negative.

Good results were seen also in dermographic urticaria. Five subjects with dermographic urticaria when retested were negative after 8 days of treatment and three showed a marked improvement. There were slight differences between these two modalities in the frequency of side effects. They consisted of headache (4 cases) and hypotension (1 case). During nimodipine treatment the headache was probably due to the pharmacological effects of nimodipine, since the literature (8) reports that this occurred for a few days in all patients from a larger patient population who were treated with nimodipine and also with the parent compound, nifedipine (11).

Only one patient had a fall in blood pressure, from 110/70 to 90/65; this has also been occasionally described in the literature (8, 16). The main side effects of terfenadine treatment were dizziness in one patient and somnolence in another.

DISCUSSION

H_1-antihistamine drugs have been used for many years in the standard treatment of physical stimulus-induced urticaria, but their effects are transient and rapidly inactivated. In the solar urticarias, as in all other physical urticarias, histamine is not the only mediator involved, and the diversity of inflammatory mediators, which at present cannot be completely evaluated, explains the frequent lack of success of antihistamine treatment (23). An effect of the calcium-antagonists on human skin mast cells is suggested by the benefit seen in a case of urticaria pigmentosa and in eight cases of chronic urticaria following nifedipine (12, 13). Other calcium-antagonists used in the treatment of urticaria are flunarizine and cinnarizine (20, 30). These agents do not affect the slow calcium channels of the miocardium, but are selective for the smooth muscle of the blood vessels (15, 32, 33). In experimental studies, cinnarizine has antihistamine, antikinin, and antiserotoninergic activities and is also an inhihitor in the skin complement sequence, especially of the fourth component (1, 9, 10). Our study examined the effectiveness of nimodipine in an open study for the treatment of 20 patients with physical stimulus-induced urticaria compared with a control group of 12 patients who received the standard treatment with terfenadine. Within 3 weeks, nimodipine showed a significantly greater clearing effect during retesting.

Our good results with high doses of nimodipine confirm the *in vitro* inhibition of the mediators from basophils by this compound and other calcium blockers. We consider that the successes obtained in symptomatic dermographism are due not only to calcium blocking of the mastocytes, but also to inhibition of the release of substance P, a neurotransmitter peptide found in the CNS and at the end of sensory nerves (3, 27). Substance P causes inflammation mediated in part by histamine and is very important for symptomatic dermographism, especially in cases that are not mediated by IgE (18).

We also wish to emphasize that the treatment was easily manageable, well tolerated and with few side effects. There were no complaints of CNS depression (loss of lucidity, somnolence, asthenia, lack of concentration), which are typical of many antihistaminics and often cause discontinuation of treatment. Until the etiopathogenesis of urticaria syndromes is clarified, we consider it useful to have an alternative to the classic treatments for symptoms. Therapeutic validity of nimodipine, or any future calcium-antagonists, needs to be confirmed in a double blind study versus placebo in a much larger patient group.

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