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Therapy of chronic idiopathic urticaria with nifedipine: Demonstration of beneficial effect in a double-blinded, placebo-controlled, crossover trial

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*The efficacy of nifedipine, a calcium channel antagonist, in the treatment of chronic idiopathic urticaria, was evaluated in a double-blinded, placebo-controlled, crossover trial. Ten patients with chronic urticaria refractory to maximally tolerated doses of H₁ and H₂ antihistamines and in whom extensive evaluation failed to identify a cause for their urticaria were entered into the study. Patients continued with their prestudy antihistamine regimens. A study drug dosage was titrated in each patient and maintained throughout the trial. Patients were treated with placebo or nifedipine for 4 weeks and then crossed over to the other medication for 4 weeks. One patient withdrew because of unrelated medical illness, two patients withdrew after crossover to placebo because of intolerable urticaria, and seven patients completed the study. A beneficial effect of nifedipine was clearly demonstrated. Hive count, hive index, and itch index were all significantly improved at the end of 4 weeks of nifedipine treatment ($p = 0.023$, 0.003 , and 0.003 , respectively) but not placebo treatment ($p = 0.194$, 0.664 , and 0.944 , respectively). Additionally, end point hive index and itch index scores with nifedipine compared to corresponding placebo scores were significantly improved ($p = 0.010$ and 0.008 , respectively). Nifedipine was well tolerated. Thus, when nifedipine is used as an adjunct to antihistamines, it appears to be a safe, efficacious drug for the treatment of chronic idiopathic urticaria. (*J ALLERGY CLIN IMMUNOL* 1989;83:756-63.)*

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Chronic idiopathic urticaria is defined as urticaria persisting for at least 6 weeks and in which a specific etiologic factor cannot be determined. The treatment of chronic idiopathic urticaria is mostly symptomatic. Histamine, released from dermal mast cells, has been implicated as an important contributory factor in the clinical manifestations of chronic idiopathic urticaria.¹⁻⁶ Evidence for such a role includes increased

Abbreviations used

t.i.d.:	Three times daily
PAF:	Platelet-activating factor
LTC ₄ , LTD ₄ , LTE ₄ :	Leukotriene C ₄ , D ₄ , and E ₄
HRA:	Histamine-releasing activity
IL-1, 3, 4:	Interleukin-1, 3, and 4

numbers of mast cells in urticarial lesions^{3,4} and elevated histamine content in skin⁵ and blister fluid^{3,6} from skin of patients with chronic idiopathic urticaria. The recent availability of additional potent H₁ antagonists,⁷⁻⁹ some of which are also nonsedating,^{7,9} has enhanced the effectiveness of antihistaminic therapy. However, in many patients, even large doses of antihistamines provide inadequate control of disease activity. For these patients, systemic corticosteroid therapy may be necessary.^{2,3} The inability to adequately control chronic idiopathic urticaria with antihistamines in a significant number of patients and the potential hazards of systemic corticosteroid therapy underscore the need for alternative medications that are safe and efficacious.

Calcium channel antagonists are a heterogeneous group of molecules that exert their pharmacologic actions by preventing an increase in intracellular calcium concentration.^{10,11} This occurs principally by inhibiting the influx of calcium ions from the extracellular compartment through membrane ion channels.^{10,11} Calcium channels may be voltage dependent and, therefore, activated by membrane depolarization or receptor regulated with activation initiated by specific agonist binding to receptors.^{10,11} Additionally, calcium antagonists may interact with cell-surface components independent of calcium channels and inhibit biochemical signals that cause mobilization of intracellular calcium stores.^{10,11} An increase in intracellular calcium concentration is critical for histamine^{10,12-17} and leukotriene secretion^{10,14} from activated mast cells. In vitro, calcium antagonists have been demonstrated to block calcium uptake¹⁷ and inhibit histamine release from rat peritoneal mast cells.¹⁷⁻²⁰ In human lung fragments, nifedipine and verapamil inhibit both histamine^{19,21-23} and leukotriene secretion.^{22,23} Nifedipine was reported to improve symptoms in a patient with urticaria pigmentosa,²⁴ a disease characterized by dermal mast cell hyperplasia in which large amounts of mast cell mediators may be released into the skin and circulation. We hypothesized that nifedipine, by possibly inhibiting the release of inflammatory mediators from mast cells, might be beneficial in the management of chronic idiopathic urti-

caria. The effectiveness of nifedipine in the treatment of chronic idiopathic urticaria was examined in a double-blinded, placebo-controlled, crossover trial.

METHODS

Experimental protocol

Ten patients with chronic urticaria (3 months to 11 years in duration) of undetermined cause and who were refractory to maximally tolerated doses of H₁ and H₂ antihistamines were entered into the study. Protocol approvals were obtained from the Human Institutional Review Boards of The Methodist Hospital and Baylor College of Medicine, and written, informed consent was obtained from each patient before study participation. The patient participation period was from Oct. 26, 1984, to Nov. 5, 1986.

Entry criteria were as follows: Urticaria must have been present for at least 6 weeks. The diagnosis of urticaria was clinical, and skin biopsies were not routinely performed. Study patients had baseline evaluation with complete history and physical examination. Radiographic studies and laboratory tests to rule out a known cause of urticaria included chest, sinus, and dental x-rays, complete blood count, SMAC 13, rapid plasma reagent, sedimentation rate, antinuclear antibody, C3, C4, total hemolytic complement, cryoglobulins, hepatitis B surface antigen, thyroid panel, serum IgG, IgM, and IgA, urinalysis, and stool for ova and parasites. Exclusion criteria included pregnancy, malignancy, diabetes, hypertension, and abnormalities in any of the above baseline studies suggestive of disease known to cause urticaria. Patients with known cardiac disease or an abnormal electrocardiogram were also excluded. Patients could not have received systemic steroid therapy for at least 4 weeks before initiation into the study. A profile of the study patients is illustrated in Table I.

The format of the treatment protocol is presented in Fig. 1. Patients were maintained with their prestudy antihistaminic regimen throughout the protocol. The study plan was divided into five phases that are described below.

Phase I consisted of a 2-week safety titration period to determine the nifedipine dose acutely tolerated by each patient up to a maximum of 20 mg t.i.d. A single 10 mg capsule of nifedipine was administered orally in the clinic, and the patient's blood pressure and pulse rate were recorded every 15 minutes for 1 hour. Any patients experiencing a drop in systolic blood pressure of 20 mm Hg or more were to be dropped from the study. Patients were discharged receiving 10 mg of nifedipine t.i.d. and returned to clinic 1 week later. If no significant side effects were reported, then a test dose of 20 mg of nifedipine was administered as described above. If this dose was tolerated, patients were discharged receiving 20 mg t.i.d. Patients who reported potential symptoms related to nifedipine continued to receive 10 mg t.i.d. for the second week of phase I or had nifedipine dosage adjusted downward as deemed necessary by the study physicians. At the end of week 2, patients were interviewed, their blood pressures were taken, and the dose of study medication to be taken during the re-

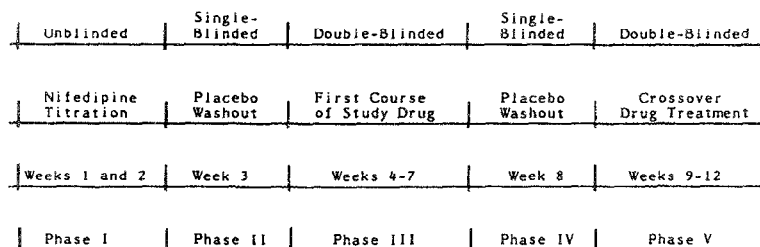


FIG. 1. Format of treatment protocol.

TABLE I. Patient profile

Patient No.	Age (yr)	Sex	Race*	Duration of urticaria	Medications for urticaria
1	25	F	W	4 yr	Hydroxyzine, diphenhydramine, cimetidine
2	38	F	B	1 yr, 4 mo	Hydroxyzine, cimetidine
3	64	F	W	2 yr	Hydroxyzine, cimetidine
4	57	F	W	13 yr	Hydroxyzine, cimetidine
5	31	F	W	7 mo	Hydroxyzine, cimetidine
6	46	M	W	1 yr, 8 mo	Hydroxyzine, cimetidine
7	19	F	B	1 yr, 4 mo	Terfenadine, hydroxyzine, cimetidine
8	42	M	W	1 yr, 3 mo	Hydroxyzine, cimetidine
9	39	F	W	10 mo	Terfenadine, ranitidine, methdilazine
10	38	F	W	5 yr	Hydroxyzine, ranitidine

*W, white; B, black.

mainder of the trial was determined. Nifedipine and placebo were provided by Pfizer in identical-appearing capsules with each capsule containing either placebo or 10 mg of nifedipine.

After completion of phase I, patients entered into the crossover trial. Patients were required to come to clinic weekly for interval history, physical examination, study medication count and replenishment, for checking the patient's diary for completeness and compliance, and for entering diary index scores into the study records.

The crossover portion of the study consisted of phases II, III, IV, and V. Phase II consisted of a 1-week placebo, patient-blinded washout and was followed by phase III, the first 4-week, double-blinded study drug period. Completion of phase III was followed by a 1-week patient-blinded placebo washout (phase IV). The study was completed with phase V during which the patient was crossed over to the other study drug.

Index scores

Patients were required to keep a daily diary record of hive index and itch index scores. The hive index was scored as follows: 0, no hives; 1, one to six hives; 2, seven to 12 hives; and 3, >12 hives. The itch index was scored as follows: 0, no itching; 1, mild itching; 2, moderate itching; and 3, severe itching. The weekly average of each of these

daily indices was calculated for each patient and used as data from which to perform statistical calculations. The term hive index or itch index in the text refers to a weekly average score.

Intradermal skin testing

Skin tests were performed before and at the completion of each 4-week study drug period. Each patient received 0.02 cc of histamine phosphate (0.275 mg/cc), compound 48/80 (0.5 mg/cc), and diluent control for each substance by intradermal injection into the volar surface of the forearm. At 15 minutes, wheal and erythema responses were measured and recorded. Antihistamines were not stopped before skin testing. Reactions caused by diluent were subtracted from histamine or compound 48/80 reactions before statistical analysis.

Statistical analysis

Hive numbers, hive index, itching index, and wheal-and-flare responses were analyzed by paired Student's *t* test analysis.

RESULTS

Ten patients were entered into the study. One patient was removed during the initial 4-week drug treatment period (phase III) because of unrelated medical prob-

TABLE II. Titration of nifedipine doses and adverse reactions in individual patients

Patient No.	Symptom	Severity	Nifedipine dose associated with side effects (mg t.i.d.)	Final nifedipine dose (mg t.i.d.)*
1	Edema	Mild	20	10
	Flushing	Mild		
	Dizziness	Mild		
2†	None		10	10
3	None		20	20
4	Orthostasis	Mild	20	10
5‡	None		10	10
6	Headaches	Mild	10	10
	Weakness/lethargy	Mild		
7	Headaches	Moderate	10	10 b.i.d.
8	Headaches	Mild	10	10
	Flushing	Mild		
9	Edema	Moderate	20	10
10	Headache	Mild	10	10
	Edema	Mild		
	Weakness/lethargy	Mild		

b.i.d., Twice daily.

*The nifedipine/placebo dose at the end of the 2-week titration period was maintained throughout the study.

†Fall in systolic blood pressure after initial dose only.

‡Refused titration to 20 mg t.i.d. for job-related reasons.

lems. Two patients asked to be withdrawn from the study because of an intolerable increase in hive activity during the first week of crossover to placebo in phase V. The other seven patients completed the protocol.

All 10 patients finished the nifedipine titration period, and in nine of these patients, at least one presumed adverse effect of nifedipine occurred. One patient (No. 2) experienced a >10 mm Hg drop in systolic blood pressure after the initial dose of nifedipine (Table II). One hour after receiving nifedipine, the systolic blood pressure had decreased from 102 mm Hg to 88 mm Hg and was accompanied by "light-headedness." This resolved with return of the patient's blood pressure to baseline 30 minutes later. Thereafter, this patient tolerated a dose of 10 mg t.i.d. throughout the 2-week titration period without difficulty. Four patients (Nos. 6, 7, 8, and 10) experienced possible nifedipine side effects while they were receiving 10 mg of nifedipine t.i.d. (Table II). In patient No. 7, the dose was decreased to 10 mg twice daily, and since symptoms were mild in the other three patients, the dose was maintained at 10 mg t.i.d. for the second week of the titration period (Table II). Symptoms believed to be related to nifedipine resolved in all four patients. Four patients (Nos. 1, 3, 4, and 9) had their nifedipine dose titrated to 20 mg t.i.d. without difficulty. Finally, one patient (No. 5) was not

titrated to 20 mg t.i.d. because of her concerns related to her job as a security officer. She was maintained with 10 mg t.i.d. The dose of study drug each patient received during the crossover period is listed in Table II. The study drug dosage did not require reduction in any patient during the crossover portion of the study. No patients were disqualified from the study because of drug intolerance.

In the seven patients who completed the trial, a beneficial, therapeutic effect of nifedipine was clearly demonstrated. A comparison of the weekly hive count, weekly hive index, and weekly itch index at the onset of the nifedipine treatment period with the end of week 4 of nifedipine treatment was highly significant in all three of these parameters of disease activity ($p = 0.023$, 0.003 , and 0.003 , respectively; $n = 7$). In contrast, neither the weekly hive count, hive index, or itch index demonstrated significant improvement from beginning to end of 4 weeks of placebo treatment ($p = 0.194$, 0.664 , and 0.944 ; $n = 7$). As illustrated in Fig. 2, there was a progressive decrease in severity of the hive index during treatment with nifedipine but not with placebo. A similar improvement was demonstrated with the itch index (Fig. 3). It is noteworthy that after 4 weeks of nifedipine treatment, both the hive and itch index scores were less than half of the starting values, whereas after 4 weeks of placebo treatment, the hive index score was

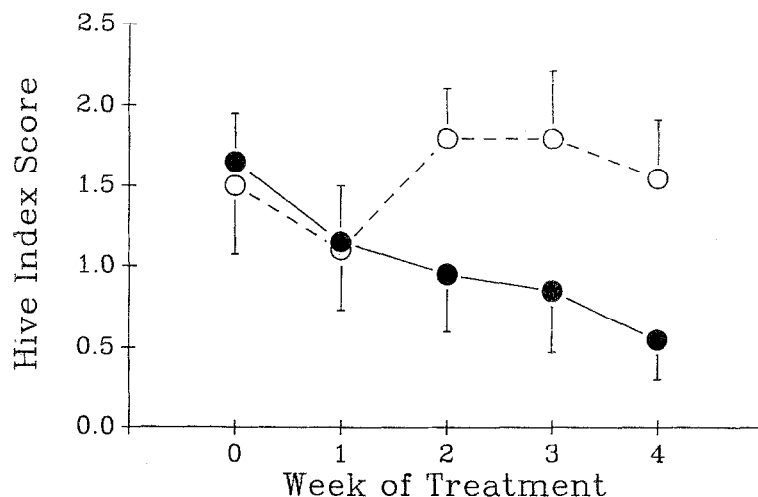


FIG. 2. Hive index during treatment with nifedipine and placebo.

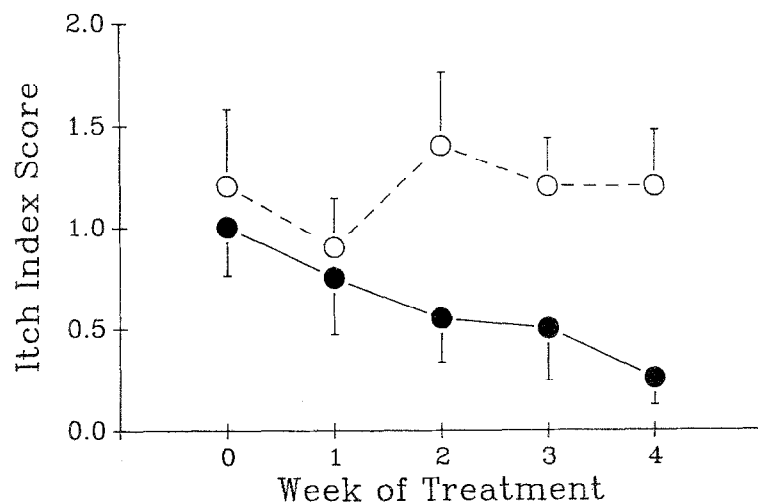


FIG. 3. Itch index during treatment with nifedipine and placebo.

minimally improved and the itch index score was slightly higher than at the start of placebo treatment (Figs. 2 and 3). Thus, patients improved with regard to hive count, hive index, and itch index while they were receiving nifedipine, whereas during the placebo treatment periods, a significant improvement was not demonstrated.

The effect of nifedipine versus placebo was also analyzed by comparison of disease activity at the end of 4 weeks of nifedipine therapy to the end of 4 weeks of placebo therapy. The end point hive count and hive index of nifedipine treatment compared with that of placebo treatment were statistically significant ($p = 0.042$ and 0.010 , respectively; $n = 7$). A similar analysis of itch index was also statistically significant ($p = 0.008$; $n = 7$). This effect was clearly a result of nifedipine treatment, since there was no statistical

significance demonstrated by a similar comparison of weekly hive count, hive index, or itch index at the beginning of placebo and nifedipine therapy ($p = 0.183$, 0.736 , and 0.605 , respectively; $n = 7$).

Erythema and wheal responses to intradermal injection of histamine and compound 48/80 were analyzed. There was no significant change in amount of histamine-induced erythema ($p = 0.352$) or wheal ($p = 0.735$) from the beginning to end of 4 weeks of nifedipine treatment. Similarly, nifedipine treatment did not result in significant differences in erythema ($p = 0.733$) or wheal ($p = 0.856$) responses with skin testing to compound 48/80.

DISCUSSION

A beneficial therapeutic effect of nifedipine on chronic idiopathic urticaria was clearly demonstrated

by this double-blinded, placebo-controlled, crossover trial. Disease activity, as measured by weekly hive count, hive index, and itch index, was significantly improved after 4 weeks of nifedipine treatment. Clinical improvement was demonstrated in a patient population with chronic urticaria of up to 13 years duration and whose urticaria was refractory to maximally tolerated antihistamines. Thus, nifedipine may be particularly useful in patients who are under consideration for systemic corticosteroid therapy because of refractory urticaria.

Two patients withdrew from the study because of increased hive activity on crossover to placebo, whereas no such exacerbations occurred after crossover to nifedipine. Of the five patients who finished phase V with nifedipine, two patients were maintained with nifedipine with good control of their urticaria. Nifedipine was stopped in two patients with subsequent exacerbation of their urticaria to levels comparable to their prestudy disease. One patient who received nifedipine in phase V was not observed in follow-up. These limited follow-up observations further supported therapeutic efficacy with nifedipine.

The most frequent side effects during nifedipine treatment were headache and edema. These symptoms have been frequently experienced by patients receiving nifedipine for treatment of cardiovascular diseases.^{25, 26} Almost all symptoms were mild, and all symptoms were manageable by reducing the nifedipine dosage. However, at higher doses, with more prolonged treatment periods, or when nifedipine is used in the presence of other diseases, the possibility of more severe adverse effects might increase.^{25, 26} It is possible that, since cimetidine may increase nifedipine blood levels,¹¹ some side effects were partially due to patients receiving H₂ antihistamines and calcium antagonists concomitantly. Likewise, the efficacy with nifedipine may have been greater than that expected from the dosage administered, since most patients were also receiving cimetidine. An important advantage of nifedipine (a dihydropyridine) over other calcium channel antagonists, such as verapamil (a phenylalkylamine), and diltiazem (a benzothiazepine)^{10, 11} in the treatment of noncardiac disease is that it has significantly less effect on the cardiac conduction system and cardiac contractility at clinically applicable doses.^{10, 11, 26}

The pharmacologic activity of calcium channel antagonists is largely attributed to inhibition of an inward flux of calcium ions through membrane channels.^{10, 11} Calcium channels may be voltage dependent and therefore activated by membrane depolarization or receptor regulated with activation initiated by specific agonist binding.^{10, 11} Classic calcium channel antag-

onists, such as nifedipine and verapamil, are more effective against voltage-dependent channels but may also inhibit receptor-mediated channel opening at higher concentrations.^{10, 11, 21} Histamine release from mast cells is dependent on a rise in intracellular calcium concentration.^{10, 12-17, 19} In rat peritoneal mast cells, nifedipine¹⁷⁻¹⁹ and verapamil¹⁸⁻²⁰ inhibited calcium uptake and histamine release. In some,^{21, 23} but not all studies,²² nifedipine and verapamil inhibited histamine release from mast cells in human lung. Inhibition of histamine release in mast cells may be at least partially mediated through receptor-regulated calcium channels, since mast cells apparently lack voltage-dependent calcium channels.^{10, 12, 13, 18, 21} Additionally, much higher concentrations of calcium antagonists were needed to significantly inhibit mast cell histamine release than to inhibit smooth muscle contraction, which is mediated by voltage-dependent calcium channels.^{10, 11, 18, 21} Furthermore, increasing the extracellular calcium concentration did not overcome inhibition of histamine release by calcium channel blockers that would be expected with voltage-dependent channels.^{10, 11, 18, 21} Finally, inhibition of histamine release by the calcium ionophore A23187 and compound 48/80, which do not use calcium channels to increase intracellular calcium concentration, supports the idea that calcium antagonists may affect histamine release through noncalcium channel mechanisms, such as membrane stabilization.¹⁸⁻²¹ The concentration of nifedipine needed to inhibit histamine release from mast cells in vitro is much greater than blood levels observed with usual doses of nifedipine.²¹ However, as was noted, cimetidine can increase nifedipine blood levels and might thereby enhance its effectiveness in vivo.

LT secretion by mast cells is also a calcium-dependent phenomenon.^{10, 14} LTC₄ is a major, if it is not the principal, lipoxygenase product of activated, dispersed human lung,²⁷⁻²⁹ gut,²⁸ and probably skin³⁰ mast cells. Intradermal injection of LTC₄, LTD₄, and LTE₄ results in a wheal and erythema response.³¹ LT secretion in vitro is inhibited by a much lower concentration of calcium antagonist drug than is histamine release,^{22, 23} and therefore, pharmacologic effects on this function might be more likely to occur in vivo.

The most prevalent cell type in many chronic urticaria lesions is the T-lymphocyte.^{3, 4} Lymphocyte proliferation to mitogen stimulation is inhibited by nifedipine and verapamil,¹⁰ and verapamil has also been demonstrated to inhibit phytohemagglutinin-induced calcium influx in lymphocytes.¹⁰ Calcium antagonism might also inhibit other sequelae of lymphocyte activation, such as the secretion of lymphokines or other biologically active molecules. For

example, peripheral blood mononuclear cells have been demonstrated to produce at least one substance with HRA for mast cells.^{4,32} Since the T cell products IL-3 and IL-4 are mast cell growth factors in the mouse,³³ IL-3 and IL-4 production by infiltrating T cells might be a contributing factor in the mast cell hyperplasia in chronic idiopathic urticaria.

Monocytes are also present in chronic urticarial lesions.^{3,4} Activated monocytes produce potent inflammatory mediators, including LTs,^{34,35} prostaglandins,³⁵ and IL-1.³⁶ IL-1 is an important promoter of lymphocyte activation, proliferation and production, and secretion of lymphokines.³⁶ Thus, an indirect role of monocytes might be stimulation of IL-3, IL-4, and HRA production by lymphocytes or production of monocyte-derived HRA. Furthermore, IL-1 has been reported to cause histamine release from mast cells.³⁷ Thus, the monocyte is also a potential target through which nifedipine might exert therapeutic effect.

PAF is an ether phospholipid produced by many inflammatory cells.³⁸⁻⁴⁰ PAF can increase vascular permeability,^{3,38} and when it is injected into the skin, it causes a wheal-and-flare response.⁴¹ However, in skin that has been depleted of histamine by repeated injections of compound 48/80, this response was markedly reduced.⁴² Although there are many possible explanations of this phenomenon, one explanation is that a significant amount of the wheal and erythema response caused by PAF is a secondary response caused by histamine release from mast cells. In fact, PAF has recently been reported to cause histamine release from mast cells.⁴³ Calcium channel antagonists have been reported to inhibit PAF binding to surface receptors on platelets and might inhibit binding of PAF to other cells, such as monocytes or eosinophils, thereby preventing cell activation by PAF.^{38,44}

Thus, there are potentially many types of cells and mediators that could contribute to the pathophysiology of chronic idiopathic urticaria. While this study was in progress, it was reported that nifedipine was effective in treating a diabetic patient with angioedema/urticaria⁴⁵ and several patients with chronic urticaria.⁴⁶ This double-blinded protocol demonstrates that nifedipine is a safe, effective adjunct to antihistamine therapy in chronic idiopathic urticaria. This is particularly important because a significant number of patients with chronic idiopathic urticaria have continued disease activity despite maximally tolerated antihistamines and may require systemic corticosteroid therapy. Additional studies will be required to characterize further optimal therapeutic conditions for the use of nifedipine in chronic idiopathic urticaria.

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