0.01, $P < 0.005$ at days 7 and 14–35, respectively; Fig. 1).

Also consistent with the above observations were the results from the clinical rating scale (Table 2). Again, the differences between the phenytoin and control groups were significant at $P < 0.05$. Finally, we noted that the quality of the scar formation was better in the phenytoin group. Our preliminary light- and electron-microscopic observations indicated that phenytoin decreases inflammation, increases fibroblast formation and wound collagen content, and stimulates neovascularization. We observed formation of excess granulation tissue in 18 patients in the phenytoin group. However, the response was controlled after cessation of topical phenytoin. No other local or systemic adverse reaction to phenytoin therapy was observed.

CONCLUSIONS

This prospectively controlled trial, the first to deal exclusively with diabetic foot ulcers, indicates that the use of phenytoin to promote healing of diabetic ulcers is both effective and safe. Its use reduced patient morbidity and hospitalization time. The hypergranulation tissue response noted in 18 patients is not only correctable but also avoidable by reducing or stopping application of powder as soon as granulation base covers the entire wound.

Given phenytoin's evident effectiveness in the promotion of wound healing, as well as its availability, low cost, ease of use, and safety, we strongly recommend its use as a treatment for diabetic ulcers. Phenytoin should prove especially useful in rural areas where daily attendance at the clinic or hospital is not possible.

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From the Department of Surgery, Madras Medical College, Madras, India.

Address correspondence and reprint requests to Jennifer De Pasquale, Health Foundation, 205 East 64th Street, Suite 404, New York, NY 10021.

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Antihypertensive Therapy With Ca^{2+} Antagonist Verapamil and/or ACE Inhibitor Enalapril in NIDDM Patients

Claudia Ferrier, MD
Paolo Ferrari, MD
Peter Weidmann, MD
Ulrich Keller, MD
Carlo Beretta-Piccoli, MD
Walter F. Riesen, PhD

Objective: To assess the efficacy and tolerance of a diuretic-free antihypertensive therapy with a Ca^{2+} antagonist and an angiotensin-converting enzyme (ACE) inhibitor in patients with non-insulin-dependent diabetes mellitus (NIDDM). Research Design and Methods: After a 2-wk washout and a 4-wk placebo phase, 47 hypertensive patients with NIDDM randomly received verapamil or enalapril alone and, if blood pressure remained elevated, both agents combined over 30 wk. Results: Verapamil or enalapril alone normalized blood pressure to <90 mmHg diastolic in 30 patients; verapamil decreased mean ± SE blood pressure from 159/98 ± 3/1 to 146/87 ± 3/2 mmHg ($n = 18$, $P < 0.001$) and enalapril from 166/99 ± 5/2 to 146/86 ± 3/1 mmHg ($n = 12$, $P < 0.001$). In 17 patients who were still hypertensive after 10 wk of monotherapy, combination of both drugs decreased blood pressure from 170/104 ± 4/2 to 152/90 ± 4/2 mmHg ($P < 0.001$). Fasting plasma glucose, glycosylated hemoglobin, serum fructosamine, total lipids, high-density and low-density lipoprotein cholesterol, apolipoproteins A-I and B, creatinine, and urinary albumin–creatinine ratio were not significantly modified. Conclusions: In hypertensive patients with NIDDM, a diuretic-free therapy based on the Ca^{2+} antagonist verapamil and/or the ACE inhibitor enalapril can effectively decrease blood pressure without

adversely affecting carbohydrate and lipid metabolism. *Diabetes Care* **14:911–14, 1991**

In the treatment of hypertension accompanying diabetes, thiazide-type or loop diuretics are problematic drugs, because they promote glucose intolerance (1) and elevate the atherogenic serum cholesterol fraction (2). β-Blockers are also not considered ideal. They decrease the awareness of hypoglycemia and may promote glucose intolerance (3), and certain β-blockers lower serum high-density lipoprotein cholesterol (2) or promote insulin-induced hypoglycemia. This study was undertaken to investigate, in a therapeutic approach avoiding diuretics and β-blockers, the blood pressure–lowering and metabolic effects of the Ca^{2+} antagonist verapamil and the angiotensin-converting enzyme (ACE) inhibitor enalapril alone or combined in hypertensive patients with non-insulin-dependent diabetes mellitus (NIDDM).

RESEARCH DESIGN AND METHODS

This study was a prospective randomized single-blind trial that was conducted over 9 mo. After written informed consent was obtained, any preexisting antihypertensive drugs were withdrawn for 2 wk. Patients whose diastolic blood pressure remained in the range of 90–115 mmHg were randomized into two groups. During 4 wk, they received placebos matching either verapamil or enalapril. Thereafter, placebo was replaced by verapamil (sustained release, 240 mg/day) or enalapril (20 mg/day). Response was defined as a decrease in diastolic blood pressure to <85 mmHg if pretreatment values on placebo ranged from 90 to 95 mmHg or to <90 mmHg if pretreatment values ranged from 96 to 115 mmHg. In nonresponders, active treatment was adjusted *1*) after 8 wk by doubling the dose of verapamil (240 mg 2 times/day) or enalapril (20 mg 2 times/day), *2*) after 10 wk by combining 240 mg verapamil and 20 mg enalapril daily, *3*) after 14 wk by doubling the dosage of the initial drug, according to randomization (480 mg verapamil or 40 mg enalapril daily), and *4*) after 18 wk by giving the double dosage of both drugs.

Patients with diastolic blood pressure >115 mmHg, proliferative diabetic or grades 3–4 hypertensive retinopathy, serum creatinine >135 μM/L, nondiabetic nephropathy, history of cerebrovascular insult, myocardial infarction or angina, heart failure, ischemic macroangiopathy, other endocrine or liver diseases, or treatment with drugs for other diseases were excluded.

Blood pressure was measured with appropriate cuff size in triplicate after resting 5 min in the supine position. Fasting plasma glucose, HbA_{1c} (by high-performance liquid chromatography), serum fructosamine, total lipids, lipoprotein cholesterol fractions (4), apolipoproteins (by enzyme-linked immunosorbent assay), electrolytes, creatinine, liver enzymes, blood cell count, and the albumin-creatinine ratio (by radioimmunoassay) in a first morning urine sample were determined after placebo and 10, 20, and 30 wk of therapy. Changes within and between groups over time were tested by two-way analysis of variance with the BMDP statistical software package.

RESULTS

Forty-nine patients started the active treatment; 47 (23 men, 24 women; mean ± SE age 58 ± 1 yr) completed the study. Known duration of diabetes and hypertension was 6.5 ± 0.8 and 9.6 ± 1.1 yr, respectively. Nine patients were treated with insulin.

Thirty patients responded satisfactorily to monotherapy with either verapamil (dose 270 ± 18 mg/day, n = 18) or enalapril (24 ± 2 mg/day, n = 12; Table 1). In 17 patients who were still hypertensive after 10 wk of monotherapy, combination of both drugs (doses 352 ± 44 and 30 ± 2 mg/day) reduced blood pressure further. Blood pressure responses did not differ between 9 insulin-treated patients and 38 not receiving insulin (−10.0 ± 2.5 and −11.5 ± 1.0%). Heart rate, body weight, hematological indices, serum sodium, potassium, and liver enzyme levels were not significantly modified by verapamil and/or enalapril.

Except for a mild decrease in fasting plasma glucose on combination therapy (Table 1), carbohydrate indices, serum total lipids and lipoprotein cholesterol fractions, and apolipoproteins A-I and B were unchanged. Total cholesterol averaged 6.4 ± 0.3 and 6.5 ± 0.4 mM/L on placebo and after 30 wk on verapamil, respectively, 6.5 ± 0.3 and 6.3 ± 0.3 mM/L before and on enalapril, and 7.6 ± 0.3 and 7.1 ± 0.4 mM/L before and on combination therapy. Corresponding values of high-density lipoprotein cholesterol were 1.3 ± 0.1 and 1.3 ± 0.1 mM/L before and after verapamil, 1.2 ± 0.1 and 1.4 ± 0.1 mM/L before and on enalapril, and 1.2 ± 0.1 and 1.3 ± 0.1 mM/L before and on combination therapy.

After 4 wk on placebo, urinary albumin–creatinine excretion ratio was within normal limits (<20 μg/mg creatinine) in 44% of patients, in the range of microalbuminuria (20–200) in 35%, and in the range of clinical proteinuria (>200) in 21%. Mean urinary albumin–creatinine excretion ratio tended to increase on verapamil and decrease slightly on enalapril, but due to large individual variations, these changes did not reach statistical significance (Table 1). Serum creatinine tended to slightly increase from 73 ± 1 to 77 ± 1 μM/L on verapamil, 81 ± 1 to 83 ± 1 μM/L on enalapril, and 81 ± 1 to 88 ± 1 μM/L on combination therapy.

Both drugs were generally well tolerated. Severe side effects were reported by only two patients who discontinued medication because of severe cough or ankle

TABLE 1
Blood pressure and some biochemical variables in hypertensive diabetic subjects on placebo and during treatment with verapamil (n = 18) or enalapril (n = 12) alone or in combination (n = 17)

		Active treatment (wk)		
	Placebo	10	20	30
Blood pressure (mmHg)				
Verapamil	159/98 ± 3/1	144/88 ± 4/2*	146/88 ± 3/2*	146/87 ± 3/2*
Enalapril	166/99 ± 5/2	147/87 ± 3/1*	143/86 ± 3/1*	146/86 ± 3/1*
Combination	170/104 ± 4/2	159/94 ± 6/1*	152/90 ± 4/2*	152/90 ± 4/2*
Plasma glucose (mM/L)				
Verapamil	9.6 ± 1.1	9.4 ± 0.8	9.0 ± 0.8	10.1 ± 1.0
Enalapril	9.0 ± 1.0	8.2 ± 0.6	8.8 ± 0.7	8.7 ± 0.7
Combination	9.6 ± 0.7	8.6 ± 0.8	8.3 ± 0.7†	8.1 ± 0.7†
Glycosylated hemoglobin (%)				
Verapamil	7.2 ± 0.5	7.4 ± 0.5	7.3 ± 0.5	7.3 ± 0.5
Enalapril	6.9 ± 0.4	6.9 ± 0.5	6.8 ± 0.4	7.1 ± 0.5
Combination	7.0 ± 0.3	7.1 ± 0.4	6.9 ± 0.4	7.3 ± 0.5
Urinary albumin–creatinine ratio (μg/mg)				
Verapamil	78 ± 32	83 ± 90	193 ± 123	251 ± 185
Enalapril	188 ± 105	112 ± 55	70 ± 50	163 ± 146
Combination	215 ± 128	204 ± 149	139 ± 74	163 ± 98

Values are means ± SE.
*P < 0.001, †P < 0.05, vs. placebo.

edema and obstipation after 2–4 wk on enalapril or verapamil, respectively.

CONCLUSIONS

This demonstrates that in hypertensive patients with NIDDM the Ca^{2+}-channel blocker verapamil and the ACE inhibitor enalapril alone or in combination are generally well tolerated and can effectively lower blood pressure without adversely affecting carbohydrate or lipoprotein metabolism. The desired blood pressure control was achieved in 87% of patients completing the 30 wk of active therapy. Comparative assessment of verapamil and enalapril, at the dosages given, suggests a nearly similar antihypertensive potency and tolerance. Age did not emerge as a codeterminant of blood pressure responses to verapamil and/or enalapril. This complements previous observations of a distinct blood pressure–lowering effect of Ca^{2+} antagonists (5,6) or ACE inhibitors (6,7) in patients with NIDDM.

The stable carbohydrate and lipoprotein indices during treatment with verapamil or enalapril in this and some previous studies in diabetic subjects (6–8) are clinically relevant. A concern that Ca^{2+}-channel blockers prescribed in clinical dosage may precipitate hyperglycemia in humans is still not entirely unwarranted but refers to a rare complication (6).

Proteinuria is an index of renal prognosis in diabetic subjects (9). Verapamil and/or enalapril did not significantly modify urinary albumin excretion in the patients with NIDDM, despite a tendency for an increase in mean urinary albumin excretion on verapamil and a slight decrease on enalapril. Previous studies were restricted largely to patients with insulin-dependent diabetes mellitus. In the latter, antihypertensive treatment with different drugs was noted to decrease *1*) protein excretion in nonazotemic incipient or clinical diabetic nephropathy (10,11) and in some (12) but not all (13) patients with azotemia and clinical nephropathy and *2*) the rate of decline in glomerular filtration rate in patients with initially nonazotemic (10,11) or mildly azotemic (12,13) clinical nephropathy. In a few normotensive insulin-dependent diabetic patients, microproteinuria was reported to decrease on captopril and increase on nifedipine (14). However, others found that some Ca^{2+} antagonists (diltiazem and nifedipine) were as effective as ACE inhibitors (lisinopril and perindopril) in decreasing clinical proteinuria and microalbuminuria in hypertensive diabetic subjects (15,16). Regardless of the exact renal protective potential of antihypertensive therapy, early initiation is more likely to produce a favorable effect, and combined blood pressure and metabolic control has top priority in the cardiovascular and renal care for diabetic patients.

From the Medizinische Poliklinik and Lipid Laboratory, University of Berne, Berne; and the Department of Endocrinology, University of Basel, Basel, Switzerland.

Address correspondence and reprint requests to Peter Weidmann, MD, Professor of Medicine, Universitäts-Poliklinik, Freiburgstrasse 3, CH 3011 Berne, Switzerland.

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Visual Impairment and Retinopathy in People With Normal Glucose Tolerance, Impaired Glucose Tolerance, and Newly Diagnosed NIDDM

Ronald Klein, MD, MPH
Elizabeth L. Barrett-Connor, MD
Barbara A. Blunt, MPH
Deborah L. Wingard, PhD

Objective: Prevalence rates of visual impairment and retinopathy were compared in 1992 people with normal glucose tolerance, impaired glucose tolerance (IGT), or newly diagnosed non-insulin-dependent diabetes mellitus (NIDDM). Research Design and Methods: Glucose tolerance status was based on an oral glucose tolerance test after exclusion of those with a history of diabetes and/or diabetes medication use in an upper middle-class community of older white adults in southern California between 1984 and 1987. Results: Although many sex-specific comparisons were made between glucose tolerance groups, only a few emerged as statistically significant. Among those, women with IGT had significantly higher age-adjusted rates of visual impairment (10.8%) than women with normal glucose tolerance (4.4%). Among men, those with IGT had significantly higher age-adjusted rates of visual impairment (7.9%) than men with newly diagnosed NIDDM (4.0%). Conclusions: Low frequencies of retinopathy were found in all three glucose tolerance groups. *Diabetes Care* 14:914–18, 1991

Cataract, glaucoma, and retinopathy are more frequent in people with known diabetes mellitus than in people who have not been diagnosed as having diabetes (1–6). These ocular conditions result in higher frequencies of visual impairment and legal blindness in diabetic people compared with people without diabetes (1,5). Little information is available that describes ocular complications, visual acuity, and rates of visual impairment in people with impaired glucose tolerance (IGT) or newly diagnosed non-insulin-