Long-Term Therapy with Slow-Release Nifedipine in Essential Hypertension

Francesco Arrigo, Fausto Consolo
Istituto Pluridisciplinare di Clinica Medica e Terapia Medica Generale e Speciale, Cattedra di Cardiologia, Policlinico Universitario G. Martino, University of Messina, Messina, Italy

Summary. The purpose of this study, designed as an open multicenter trial, was to test the antihypertensive efficacy, patient acceptability, and side effects of long-term treatment with slow-release nifedipine in a large population. The drug was studied in 330 outpatients with essential hypertension, WHO stage 1–2, recruited in 20 hospital centers. After washout period was completed, nifedipine (20 mg bid) was given for 1 month (phase 1). Then, the treatment was extended for 4 months (phase 2) with variable doses (range 20–80 mg daily). No other antihypertensive drugs were administered during phase 1. However diuretics, beta blockers, or captopril were added to nifedipine during phase 2 in 11 patients. Seventy patients did not meet criteria for inclusion at washout. During phase 1 and 2, 66 additional patients were excluded due to side effects, the need of other antihypertensive drugs, or non-compliance. Systolic blood pressure significantly lowered (10% or more) in 84% patients in phase 1 and in 76% in phase 2. No responders were 6.1% and 3.6%, respectively. Diastolic blood pressure was normalized in 60% of patients after 5 months of therapy. Effects on blood pressure were equal in young patients and in the elderly, but a minimal rise in heart rate was recorded in younger patients.

At least one side effect occurred in 46.6% patients, mainly headache (15.4%), hot flashes (13.3%), ankle edema (12.8%), or palpitation (6.6%). Sixteen patients (8.2%) were obliged to stop nifedipine treatment due to the severity of the side effects. This trial confirms the efficacy of nifedipine in hypertension, both in young and in aged patients. The adherence of patients to the twice-daily regimen was very good, without the development of tolerance in long-term treatment. The drug does not affect the physiologic cardiovascular response to standing, but induces several relatively common, very seldom severe, adverse reactions.

Key Words. nifedipine, hypertension, elderly hypertensives

Calcium-channel blockers have antihypertensive efficacy due to their vasodilator effect, and their use in the treatment of hypertensive patients is increasing [1–3]. Nifedipine differs from other nondihydropyridine calcium-channel blockers because of its more potent vasodilating effect [4,5] and the absence of a clinically evident negative inotropic action. Although the antihypertensive action of nifedipine was first proved in 1972 [6,7], its use in long-term therapy was not widespread due to its short half-life and brief duration of action.

More recently, slow-release nifedipine, a crystal-line preparation with delayed enteral absorption, has been available for clinical use and this form overcomes some of the previous limitations. One slow-release nifedipine tablet produces constant plasma concentrations and reduces blood pressure over 9–10 hours [8]. These properties suggest the drug could be administered only twice daily, thus reducing adverse reactions and improving patient acceptance. Nevertheless, few clinical studies on slow-release nifedipine have been completed.

The purpose of this study, designed as an open multicenter trial, was to evaluate the antihypertensive efficacy, side effects, and patient acceptance of long-term therapy with slow-release nifedipine in a large population.

Methods

Slow-release nifedipine was studied in outpatients with primary, untreated hypertension or who had not taken drugs for at least 2 weeks. The study was carried out in 20 hospital centers, and each center recruited 20 hypertensive patients.

The following criteria were used for inclusion in the study: a) age range, 30–75 years; b) blood pressure above 165/95 mmHg in three repeated measurements in supine position; c) no secondary hypertension revealed by routine procedures; d) no clinical evidence of heart failure, A-V block, severe obstructive arterial disease, pregnancy, or malignancy; and e) WHO stage 1 (uncomplicated hypertension) or 2 (at least one target organ damaged). The purpose and design of the investigation were explained to patients, and informed consent was obtained.

Address for correspondence and reprint requests: Prof. Francesco Arrigo, via P Longo 2/a, 98100, Messina, Italy.
The study design included three phases: 2 weeks with no antihypertensive drugs (washout); 1-month treatment with constant slow-release nifedipine at a dose of 20 mg bid (phase 1); and a 4-month treatment with variable slow-release nifedipine doses (phase 2). Only patients fitting established criteria at the end of the washout period were admitted to the treatment. Some few patients with unsatisfactory effect during phase 1 were treated with increased doses of the drug, while patients needing other antihypertensive drugs were excluded from the study. During phase 2, the drug dosage was individually adjusted (20–80 mg/day) to achieve a better effect and other drugs (diuretics, beta blockers, or captopril) were added in some patients.

All patients were evaluated at the end of washout, at the end of phase 1, and after 2 and 4 months during phase 2. Each clinical evaluation included an interview and measurements of body weight, heart rate, and arterial blood pressure. Blood pressure (cuff-stethoscope method) and heart rate were measured after 5 minutes of rest in the supine position and after 2 minutes standing. Care was taken to record any pharmacologic therapy performed and any patient’s complaint that might be due to the drug.

The laboratory examination—performed after washout and at the end of phase 2—comprised urinalysis, blood cell counts, hemoglobin, plasma electrolytes, serum glucose, creatinine, uric acid, cholesterol, triglycerides, gamma-glutamyl-transpeptidase, blood urea, creatinine clearance, standard 12-lead electrocardiogram, fundus oculi, and chest roentgenogram.

The efficacy of the treatment was rated by at least a 10% reduction in systolic blood pressure and by a reduction in diastolic blood pressure to < 90 mmHg. The percentage of responders and the changes in blood pressure, heart rate, and blood pressure are reported in Table 1. Both systolic and diastolic blood pressure reduced significantly (p > 0.001) after 1 month and fell further after 5 months. Normalization of diastolic blood pressure was achieved in 32.7% of patients after 1 month and in 60% after 5 months, while the number of no responders was 6.1% and 3.6%, respectively. Responders with a 10% reduction of systolic blood pressure were 84% in phase 1 and 76% in phase 2.

In the age subgroups, no differences were found between patients over and under 60 years (Table 2). However, younger patients manifested little but significant elevation in heart rate.

ECG, ocular fundus, chest x-ray, and laboratory values were all unchanged, except for uric acid, serum cholesterol, and triglycerides (Table 3).

Adverse reactions were evaluated in patients not taking drugs other than nifedipine (Table 4). Ninety-one patients (46.6%) had at least one side effect, but only a few had more than one. Sixteen patients (8.2%) stopped treatment because of severe side effects. Headache, mild in 26 and strong in four cases, was the most frequent complaint, often associated with hot flashes and flushing of the face. The most common unwanted effect was ankle edema, observed in 25 patients. In these cases body weight was unchanged and administration of diuretics relieved the disturbance in four patients. Patients suffering from palpitations manifested slightly increased (nine cases) or normal (two cases) heart rate, while two patients showed an obvious sinus tachycardia. Cutaneous rash (three cases) led to treatment interruption that resulted in complete recovery in a few days. Rare side effects included salivation, and leg pain at rest in one case with obstructive arterial disease, hiccuping, tremor, tinnitus, and weakness.

The drop-out rate was 20% in the total group of cases were excluded due to side effects or the addition of other drugs and 16 patients did not undergo control visits; therefore, 282 cases entered phase 2 treatment. During phase 2, four patients withdrew because of side effects, while two cases needed drugs other than diuretics, captopril, or beta blockers, and 12 others missed follow-up appointments. The remaining 264 patients were included in the final evaluation.

In 189 cases (71.6%) the nifedipine dose of 40 mg/ day was kept constant. Out of the remaining patients, 17.4% were treated with variable doses (20–80 mg/ day) and 11% received 60 mg/day of nifedipine plus other drugs. These three groups did not differ in age or sex; the hypertension duration was longer, and the WHO stage was higher in patients needing other drugs.

The values of body weight, supine and standing heart rate, and blood pressure are reported in Table 1. Both systolic and diastolic blood pressure reduced significantly (p > 0.001) after 1 month and fell further after 5 months. Normalization of diastolic blood pressure was achieved in 32.7% of patients after 1 month and in 60% after 5 months, while the number of no responders was 6.1% and 3.6%, respectively. Responders with a 10% reduction of systolic blood pressure were 84% in phase 1 and 76% in phase 2.

In the age subgroups, no differences were found between patients over and under 60 years (Table 2). However, younger patients manifested little but significant elevation in heart rate.

ECG, ocular fundus, chest x-ray, and laboratory values were all unchanged, except for uric acid, serum cholesterol, and triglycerides (Table 3).

Adverse reactions were evaluated in patients not taking drugs other than nifedipine (Table 4). Ninety-one patients (46.6%) had at least one side effect, but only a few had more than one. Sixteen patients (8.2%) stopped treatment because of severe side effects. Headache, mild in 26 and strong in four cases, was the most frequent complaint, often associated with hot flashes and flushing of the face. The most common unwanted effect was ankle edema, observed in 25 patients. In these cases body weight was unchanged and administration of diuretics relieved the disturbance in four patients. Patients suffering from palpitations manifested slightly increased (nine cases) or normal (two cases) heart rate, while two patients showed an obvious sinus tachycardia. Cutaneous rash (three cases) led to treatment interruption that resulted in complete recovery in a few days. Rare side effects included salivation, and leg pain at rest in one case with obstructive arterial disease, hiccuping, tremor, tinnitus, and weakness.

The drop-out rate was 20% in the total group of