Antihypertensive and Metabolic Effects of Amlodipine in Patients with Non-Insulin-Dependent Diabetes Mellitus

T.M. Seccia, V. Vulpis, S. Ricci and A. Pirrelli
DIMO, Department of Internal Medicine, University of Bari, Italy

Summary

The aim of this study was to evaluate the antihypertensive efficacy and possible effects on metabolic control of amlodipine in hypertensive diabetic patients. After a washout period of 4 weeks, 28 ambulatory patients with mild essential hypertension and non-insulin-dependent diabetes mellitus received amlodipine 10mg once daily for 12 weeks. Blood pressure was significantly decreased after 2, 4, 8 and 12 weeks of treatment when compared with basal values. No significant changes in heart rate occurred. A significant decrease in fasting plasma glucose was evident after 12 weeks. A slight but not significant decrease in pre- and postprandial plasma glucose, glycosuria and fructosamine concentrations occurred after 4 and 12 weeks of treatment. Microalbuminuria decreased significantly at the end of the study. No correlation was found between the reduction in microalbuminuria and the reduction in systolic or diastolic blood pressure. Cholesterol concentrations and triglycerides decreased, although only the latter was significant. The results of this study confirm the antihypertensive efficacy of amlodipine in hypertensive diabetic patients, and suggest a favourable influence of this drug on glycaemic and lipid control. The favourable changes in microalbuminuria observed after treatment need further studies to elucidate both the exact mechanisms behind increased microalbuminuria in the hypertensive diabetic state and the factors involved in the reduction.

A higher incidence of arterial hypertension has been reported in the literature among diabetic patients than in normal subjects. Furthermore, cardiovascular risk is twice as high in diabetics with concomitant hypertension. Antihypertensive treatment has been prescribed in these patients, although associated side effects can occur, reducing the therapeutic advantages. Calcium antagonists and ACE inhibitors are widely used in such patients. In particular, dihydropyridines are a biochemically heterogeneous group of drugs able to inhibit the transmembrane influx of calcium ions (Ca++) into cells by binding with the voltage-operated channels. Their activity is clinically relevant
in cardiac and smooth muscle cells, in which they interfere with Ca++ current and excitation-secretion coupling.

New analogues with different pharmacological properties have been recently synthesised to improve the antihypertensive effectiveness, tolerability and therapeutic compliance profile. Amlodipine, a dihydropyridine derivative with pharmacokinetics that are both qualitatively and quantitatively different from the other available dihydropyridines, is considered a representative example of the novel drugs of this group.

As insulin release from the pancreatic β cell is coupled with calcium entry,¹⁸⁻¹⁰ and since calcium antagonists can affect the secretory activity of this hormonal substance, they can unfavourably influence the concomitant diseases associated with diabetic hypertensive patients.

Even subtle differences in the chemical structure of a drug can be of great importance as these differences can affect both the affinity for the drug’s receptors and the postbinding molecular events. It is therefore appropriate to investigate the metabolic effects whenever a new calcium antagonist is introduced into clinical practice. This study was thus undertaken to evaluate the antihypertensive efficacy and possible effects on the metabolic control of amlodipine in hypertensive diabetic patients.

Patients and Methods

Patients

28 ambulatory patients (17 male, 11 female; mean age 54.5 ± 9.4 years) with mild, uncomplicated essential hypertension and non-insulin-dependent diabetes mellitus (NIDDM) of at least 6 months’ duration were included in the study. Informed consent was obtained from each patient. Ethical approval was obtained from the Ethics Committee of the University of Bari, Italy.

Criteria set down by the National Diabetes Data Group¹¹ were followed to identify the patients with NIDDM.

Methods

Before enrolment into the study, most patients were not responding to or were experiencing problems with tolerance on their current antihypertensive medication, which consisted mainly of β-blockers, ACE inhibitors or calcium antagonists. The patients (n = 19) that were treated with oral hypoglycaemic agents were allowed to continue their current medication; prior antihypertensive treatment or any other drugs were discontinued at the beginning of the study. Thus, after a washout period of 4 weeks, study participants received amlodipine 10mg once daily for 12 weeks.

Systolic (SBP) and diastolic (DBP) blood pressure, both supine and upright, and heart rate (HR) were measured at the beginning of the study (t₁), at the end of the washout period (t₀), and after 2 (t₁), 4 (t₂), 8 (t₃) and 12 (t₄) weeks of treatment. Blood pressure was recorded twice using a mercury sphygmomanometer in the morning, after 15 minutes in the supine position and after 2 minutes in the standing position; mean values were reported. DBP was taken at Korotkoff phase V. The values were recorded 3 to 8 hours and 24 hours after the morning drug intake.

At t₁ the patients were asked to continue their normal diet and to avoid changes throughout the study. The glycaemic profile (fasting: in the morning before breakfast; prelunch: 30 minutes before lunch; postlunch: 2 hours after lunch; predinner: 30 minutes before dinner), microalbuminuria and glycosuria were measured at t₀, t₂ and t₄; serum fructosamine levels, a reliable index for blood glucose control, were also measured, spanning a period of 2 to 3 weeks.

ECG and routine haematological and biochemical laboratory tests (serum levels of urea, creatinine, uric acid, total and high density lipoprotein cholesterol, triglycerides, alanine transaminase, aspartate transaminase, alkaline phosphatase, total bilirubin, total protein, haemelanaysis and urinalysis) were performed at t₀ and t₄. Fructosamine was measured by Johnson’s colorimetric method;¹² microalbuminuria was measured using an immunoturbidimetric method, whereby low concen-