Journal of the American Society of Hypertension 10(3) (2016) 244–251

Research Article

Differential effects of enalapril–felodipine versus enalapril–lercanidipine combination drug treatment on sympathetic nerve traffic and metabolic profile in obesity-related hypertension

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Manuscript received November 23, 2015 and accepted January 5, 2016

Abstract

Scanty information is available on the effects of combination drug treatment based on an ACE inhibitor and a calcium channel blocker on the neurometabolic alterations characterizing obesity-related hypertension (OHT). After 2-week run-in with enalapril (20 mg), 36 OHTs were randomized according to a double-blind crossover design to a combination therapy with either lercanidipine 10 mg (L) or felodipine extended release 5 mg (F), each lasting 8 weeks. Measurements included clinic and ambulatory blood pressure (BP) and heart rate, homeostasis model assessment index, plasma norepinephrine, and muscle sympathetic nerve activity. Patients with uncontrolled BP were then uptitrated to 20 mg/d (L) and 10 mg/d (F) combined with enalapril 20 mg, respectively, for further 8 weeks. For similar BP reductions, enalapril–lercanidipine (EL) caused norepinephrine and MSNA increases significantly less pronounced than those seen with enalapril–felodipine, the lesser sympathoexcitation observed with EL being coupled with a significant improvement in homeostasis model assessment index. This was the case also when L and F were uptitrated in the combination. In OHT, at variance from enalapril–felodipine, EL combination is almost entirely devoid of any major sympathoexcitatory effect and is associated with an improvement in insulin sensitivity. J Am Soc Hypertens 2016;10(3):244–251.

Keywords: Combination drug treatment; lercanidipine; obesity-related hypertension; sympathetic activity.

Introduction

Obesity-related hypertension represents a clinical condition characterized by a high or a very high cardiovascular risk, the abnormal values of body fat depot as well as blood pressure (BP) being frequently associated with major cardiovascular complications and presence of end-organ damage, metabolic abnormalities, insulin resistance, endothelial dysfunction as well as neuroadrenergic activation.[1–10] This latter alteration appears to be of key pathophysiological relevance and a major target of the therapeutic intervention considering that in obesity-related hypertension sympathetic neural mechanisms (1) contribute at the development and progression of the high BP state and the related target organ damage,[3,4,7–10] (2) participate at the occurrence of metabolic alterations,[3,4,7,9,10] and (3) concur with other factors at determining the cardiovascular complications as well as the cardiovascular outcome of the obese state associated with hypertension, including sudden cardiac death.[5,6,9,10] Scanty, however, is the information

Conflict of interest: None.
Funding: None.

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1933-1711/$ - see front matter
http://dx.doi.org/10.1016/j.jash.2016.01.006

available on the effects of antihypertensive drug treatment on neuroadrenergic function in patients in which hypertension is complicated by obesity.[5–7] This is particularly the case for the combination drug treatment based on an ACE inhibitor and a calcium antagonist, that is, the therapeutic approach recommended by current guidelines and most commonly used in the treatment of this clinical condition.[6]

The present study was designed at providing information on this issue. In particular, the study was aimed at comparing the long-term effects of two different combination drug regimens, both based on an ACE inhibitor and a calcium antagonist, that is, enalapril–felodipine (EF) and enalapril–lercanidipine (EL), on sympathetic cardiovascular drive, as assessed by the only approach available so far to directly and continuously measure in humans sympathetic neural discharge, that is, the microneurographic technique.[2,5,6]

Methods

Study Population

The study population consisted of 45 obese hypertensive patients of both sexes (33 men and 12 women) recruited from our outpatient clinic. However, because of the inability to obtain stable muscle sympathetic nerve activity (MSNA) in all experimental sessions (see below), the study was successfully carried out in 36 patients. They reported BP values consistently higher than 140/90 mm Hg on ACE inhibitor monotherapy at repeated sphygmomanometric measurements and displayed body mass index (BMI, body weight divided by the square of height) between 30 and 40 kg/m^2. All patients were in sinus rhythm, occasionally alcohol drinker, and none was a cigarette smoker. Coronary heart disease, congestive heart failure, cerebrovascular disease, renal insufficiency, diabetes mellitus, respiratory diseases, or other conditions known to affect autonomic function[5,6] were ruled out on the basis of clinical evidence or appropriate biochemical or instrumental work-up. Obstructive sleep apnea of mild-to-moderate degree was detected via overnight polysomnography in 16 of the 36 patients who completed the study. No patient was involved in a physical training or in a body weight reduction program. The protocol of the study was approved by the Ethics Committee of the Istituto Auxologico Italiano and the IRCCS Mutimedica, Sesto San Giovanni, Milan, Italy. All patients gave written consent to the study after detailed explanation of its nature and purpose.

Study Design

After recruitment, patients entered a 2-week run-in period during which they discontinued previous ACE inhibitor treatment and were switched directly to enalapril 20 mg once daily in the morning. The study proper consisted of four identical experimental sessions within a randomized double-blinded crossover design (see below, Figure 1). Following the first experimental session, the patients were randomly allocated according to a computerized list to take a morning oral dose of felodipine extended release (5 mg, 18 patients) or lercanidipine (10 mg, 18 patients) added to the already administered enalapril 20 mg/d for an 8-week period. This was followed by the second experimental session, carried out according to a protocol identical to the one described for the first session (see below). Felodipine or lercanidipine administration was then discontinued, and the patients remained for a 2-week period under enalapril 20 mg/d treatment. This was followed by a second 8-week period during which the patients received at the dosage above mentioned the calcium antagonist drug not taken in the first 8-week period and added to enalapril treatment. A third experimental session was then performed, according to the same protocol of the two previous experimental sessions. A 24-hour ambulatory BP was performed before and at the end of the first 8-week treatment and assessed again following the second 8-week treatment. Finally, in the patients with persistent uncontrolled BP at the visit carried out after the second treatment period, the assigned daily dose of drugs was uptritated to enalapril 20 mg/felodipine 10 mg (n = 14) or enalapril 20 mg/lercanidipine 20 mg (n = 13), according to a single blinded design. This treatment period, lasting again 8 weeks, was followed by a final experimental session, in which, with the exception of 24-hour ambulatory BP monitoring, the previously mentioned variables were reassessed. During each period, patients were seen at a 2-week interval in the outpatient clinic of our hospital. No lifestyle changes were advised. Pills count was performed at each visit with new medications dispensed.

Measurements

Measurements included BMI, waist-to-hip ratio, sphygmomanometric, beat-to-beat finger (Finapres; Ohmeda 2300, Englewood, Florida, USA) systolic BP, diastolic BP, heart rate (HR; electrocardiogram), respiration rate (pneumotachograph), and echocardiographically detected left ventricular mass index, calculated by the Devereux formulae normalized to body surface area.[11,12] They also included multiunit recordings of muscle sympathetic nerve traffic (MSNA) via the microneurographic technique, as previously described,[2,7,13] venous plasma norepinephrine (NE) measured by high-performance liquid chromatography,[14] and fasting plasma glucose and plasma insulin, which were determined from a blood sample taken from an antecubital vein. From a standard formulae (plasma insulin × fasting plasma glucose/22.5), calculation was made of the homeostasis model assessment (HOMA) of