Journal of the American Society of Hypertension 9(7) (2015) 526–535

Research Article

Ambulatory 24–hour cardiac oxygen consumption and blood pressure–heart rate variability: effects of nebivolol and valsartan alone and in combination

Joseph L. Izzo, Jr., MD*, Safi U. Khan, MBBS, Osman Saleem, MD, and Peter J. Osmond, MS

Department of Medicine, State University of New York at Buffalo, Erie County Medical Center, Buffalo, NY, USA

Manuscript received December 29, 2014 and accepted March 23, 2015

Abstract

We compared an angiotensin receptor blocker (valsartan; VAL), a beta–blocker (nebivolol; NEB) and the combination of NEB/VAL with respect to 24–hour myocardial oxygen consumption (determined by 24–hour ambulatory heart rate–central systolic pressure product [ACRPP]) and its components. Subjects with hypertension (systolic blood pressure >140 or diastolic blood pressure >90; n = 26) were studied in a double–blinded, double-dummy, forced–titration, crossover design with 3 random-order experimental periods: VAL 320 mg, NEB 40 mg, and NEB/VAL 320/40 mg daily. After 4 weeks of each drug, ambulatory pulse wave analysis (MobilOGraph) was performed every 20 minutes for 24 hours. All three treatments resulted in nearly identical brachial and central systolic blood pressures. NEB alone or in combination with VAL resulted in lower ACRPP (by 11%–14%; $P < .001$ each) and heart rate (by 18%–20%; $P < .001$ each) compared with VAL, but stroke work (ACRPP per beat) was lower with VAL. Relative and adjusted variability (standard deviation and coefficient of variation) of heart rate were also lower with NEB and NEB/VAL than VAL. Results in African Americans, the majority subpopulation, were similar to those of the entire treatment group. We conclude that the rate–slowing effects of NEB cause ambulatory cardiac myocardial oxygen consumption to be lower with NEB monotherapy or NEB/VAL combination therapy than with VAL monotherapy. NEB/VAL is not superior to NEB alone in controlling heart rate, blood pressure, or ACRPP. Heart rate variability but not ACRPP variability is reduced by NEB or the combination NEB/VAL. There is no attenuation of beta–blocker–induced rate–slowing effects of in African Americans. J Am Soc Hypertens 2015;9(7):526–535.

Keywords: Ambulatory blood pressure monitoring; angiotensin receptor blockers; beta blockers; central blood pressure; clinical trial; myocardial oxygen consumption; nebivolol; pulse wave analysis; rate-pressure product; valsartan.

Introduction

The key to effective drug therapy in hypertension is choosing appropriate combinations of medications.[1] In general, it is most efficient to combine drugs with widely divergent mechanisms of action; for example, fully additive effects are seen when a thiazide diuretic is combined with an angiotensin–converting enzyme inhibitor.[1] It is not clear, however, whether combining drugs that block the renin–angiotensin system (RAS), such as a beta–blocker and an angiotensin receptor blocker (ARB), is a useful strategy to reduce blood pressure (BP) or cardiovascular disease (CVD) risk.[1] There are several unanswered questions. Both of these RAS blockers exhibit similar antihypertensive efficacies, but their hemodynamic mechanisms are different,[2] raising the question whether they have differential effects on myocardial oxygen consumption (MVO2). Another issue is whether the hemodynamic effects traditionally demonstrated in the laboratory are present in the ambulatory environment. It also remains unclear whether central (aortic) systolic pressure is better indicator of therapeutic benefit than traditional brachial cuff BP values.[3]

Conflict of interest: none.

The study was funded by Forest Laboratories but was designed, conducted, analyzed, and reported in its entirety by the PI without interference or comment from the sponsor.

*Corresponding author: Joseph L. Izzo, Jr., MD, Department of Medicine, State University of New York at Buffalo, Erie County Medical Center, 462 Grider St, Buffalo, NY 14215. Tel: 716-898-5625; Fax: 716-898-4493.

E-mail: jizzo@buffalo.edu

1933-1711/$ - see front matter
http://dx.doi.org/10.1016/j.jash.2015.03.009

Another unanswered question is whether abnormal BP variability, which has been associated with increased risk of stroke[4] and CVD,[5] differs between drugs.[6] Finally, older people[7] and African Americans[8] exhibit reduced antihypertensive efficacy with RAS blocker monotherapy, and the heart rate and hemodynamic effects of beta–blockers and ARBs are not well described in these populations.

It is now possible to address these questions by performing 24–hour ambulatory oscillometric pulse wave analysis (IEM Mobil–O–Graph, Stolberg, Germany).[9,10] We focused primarily on ambulatory central rate–pressure product (ACRPP) and its components over 24 hours and during the daytime and nighttime periods. The primary hypothesis was that NEB/VAL combination therapy would be superior to VAL monotherapy in reducing mean 24–hour cardiac MVO2, and secondarily, that monotherapy with NEB would be superior to monotherapy with VAL. Another secondary hypothesis was that NEB, alone and in combination, would reduce the variability of heart rate and 24–hour cardiac MVO2.

Methods

Study Subjects

All subject signed informed consent forms and were monitored by the Health Sciences Institutional Review Board of the University at Buffalo. Males and females, 18 years or older with chronic hypertension, treated or untreated, were included if their seated mean clinic systolic BP was 145–179 mm Hg, inclusive, or clinic diastolic BP 92–119 mm Hg, inclusive. Subjects with any of the following conditions were excluded: history of clinically significant adverse events with beta–blocker or ARB; any acute or chronic medical condition that, in the judgment of the investigator, rendered the subject unable to complete the study, would interfere with optimal participation in the study, or cause significant risk to the subject; concomitant or probable need for treatment with other cardiovascular or antihypertensive drugs that may affect BP or influence the effects of study drugs, (eg, diuretics or high–dose nonsteroidal anti–inflammatory drugs); known ischemic heart disease requiring continuous beta–blocker therapy (includes angina, prior transmural myocardial infarction, coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty or stenting within 6 months prior to study entry); dilated cardiomyopathy (New York Heart Association Functional Class II–IV); clinically significant valvular heart disease or obstructive hypertrophic cardiomyopathy; pre-existing bradycardia (heart rate $<$60 beats/min); presence of clinically significant ventricular or supraventricular arrhythmias (eg, atrial fibrillation/flutter), pre–excitation syndrome, second or third degree atrioventricular block, other conduction defects necessitating the implantation of a permanent cardiac pacemaker, or sick sinus syndrome; chronic kidney disease (serum creatinine $>$2.5 mg/dL); known or suspected secondary hypertension (eg, renovascular hypertension, primary hyperaldosteronism, etc.); uncontrolled diabetes mellitus (hemoglobin A1c $>$10%); history of alcohol or other drug abuse within 6 months prior to enrollment; positive pregnancy test or failure to practice adequate contraception in women of child–bearing potential. Use of beta agonist inhaler was permitted on an as–needed basis, but not within 72 hours of an ambulatory BP monitoring study.

Qualification Period

To allow subjects to safely meet the target BP range, qualification could be extended up to 3 weeks prior to randomization (week 0). Untreated subjects could enter the experimental phases of the trial directly (week 0). At the discretion of the investigator, controlled individuals could have all therapy withdrawn, while others remained on one– or two–drug therapy for the remainder of the qualification period (maximum of 3 weeks). Those on prior beta–blocker therapy were stepped down prior to entry, with doses halved at 3–day intervals (eg, metoprolol succinate 200, 100, 50, 25 mg/day; atenolol 100, 50, 25 mg/day; carvedilol–CR 40, 20 mg/day; nebivolol 40, 20, 10, 5 mg/day) until subjects reached the lowest doses for each agent. All prior antihypertensive medications were stopped by week 0.

At or before the randomization visit (week 0; see Figure 1), subjects had a full history and physical exam, electrocardiogram, and urine pregnancy test if female with child–bearing potential. Hemoglobin A1c and serum creatinine were drawn in anyone with history of diabetes or chronic kidney disease, unless there was a value within the past 3 months of $<$10% or $<$2.5 mg/dL, respectively. Subjects were excluded in the qualification period if BP exceeded the safety limits ($<$180 mm Hg systolic or $\leq$120 mm Hg diastolic) prior to receiving study medication.

Experimental Design

The protocol was a double–blinded, double-dummy, forced–titration, random–order–entry crossover design with three experimental periods and 10 clinic visits (Figure 1). Because the primary dependent variable was a comparison between valsartan and the valsartan/nebivolol combination, no placebo period was necessary. The random order entry approach was necessary to minimize potential bias caused carry–over effects from prior treatments; this created six possible drug sequences for the three experimental periods (Figure 1). To provide a margin of safety within each experimental period, there was a 1–week period of forced titration starting with half–maximal doses