

# Supplements Tested for Nocturnal Hypertension

BY ERIK GOLDMAN  
Contributing Writer

MADRID — Melatonin supplementation can improve nocturnal blood pressure control and prevent early morning pressure surges in hypertensive patients who do not show the typical nighttime pressure drop, according to results presented at the annual meeting of the European Society of Hypertension.

But another dietary supplement—vitamin E—was shown to increase blood pressure in diabetic hypertensive patients in a second study reported at the meeting.

“Impaired nocturnal blood pressure fall is associated with increased risk of target organ damage related to hypertension,” said Dr. Yehonatan Sharabi of the Chaim Sheba Medical Center, Tel Hashomer, Israel, presenting the melatonin study.

It is not clear why some patients fail to show the usual nighttime pressure drop, but lack of melatonin, a hormone secreted by the pineal gland, may play a role. In patients with a blunted nocturnal blood pressure fall, the amount of urinary 6-sulfatoxymelatonin, the key metabolite of melatonin, is markedly reduced.

The Israeli team, with researchers at Gazi University, Ankara, Turkey, tested melatonin in 38 nonobese hypertensive patients already on one or more antihypertensive drugs. They were generally well controlled except for the impaired nighttime pressure fall and increased early morning pressure surges. Mean age was 64 years, with a range of 42-83 years. Those with insomnia were excluded.

After a 2-week placebo run-in period, the patients underwent baseline 24-hour ambulatory pressure monitoring, then were randomized to either 2 mg of controlled-release melatonin per day or placebo. They were instructed to take the assigned tablet 2 hours before bedtime. After 4 weeks, they underwent 24-hour monitoring. At baseline, the melatonin patients had mean morning pressures of 141/78 mm Hg and mean nighttime pressures of 136/72 mm Hg. The placebo group showed similar baseline values.

There were no significant changes in daytime systolic pressure in response to melatonin. But nighttime pressures showed a mean drop of 7 mm Hg systolic and 3 mm Hg diastolic in the melatonin group. There was no such change in the placebo group.

“The time interval from 1 a.m. to 5 a.m. seemed to be the period of maximal melatonin effect on blood pressure, and this is very important, given the incidence of early morning cardiovascular events,” said Dr. Sharabi. No adverse effects were associated with melatonin, and compliance was high, he said.

In a separate study, vitamin E induced substantial increases in mean daytime and nighttime blood pressures in diabetic patients with hypertension, compared with those who were given a soy oil placebo, reported Dr. Ian B. Puddey of the department of medicine, University of Western Australia, Perth.

Although the supplements reduced oxidative stress, as indicated by consistent falls in urinary isoprostane (a marker of oxidative stress), this presumable benefit is nullified by the unexpected rise in systolic and diastolic pressures, as well as pulse pressure and pulse rate.

After a 3-week run-in period, 55 patients with type 2 diabetes and hypertension were randomized to placebo (soy oil stripped of all tocopherols), 500 mg/day of alpha-tocopherol, or 500 mg/day of mixed gamma-, alpha-, and delta-tocopherols. About half of the patients were on at least one antihypertensive drug; two-thirds were on lipid-lowering drugs.

“Contrary to our central hypothesis, we observed a small fall in blood pressure in the placebo group but increased mean pressures in both the alpha-tocopherol and mixed tocopherol groups,” said Dr. Puddey, who presented the data on behalf of the lead investigator, Dr. N.C. Ward. The mean increase was 7 mm Hg systolic and 5 mm Hg diastolic for the patients treated with vitamin E. The 24-hour ambulatory profile showed a sustained and consistent pressure increase throughout the day, with no diurnal variation. ■

# Drug Combinations Can Quell Refractory Hypertension

BY ROBERT FINN  
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ATLANTA — Stubbornly refractory hypertension can be approached with a number of drug combinations and other novel treatments, Dr. Angela L. Brown said at a meeting sponsored by the International Society on Hypertension in Blacks.

The combination of a diuretic and an inhibitor of the renin-angiotensin-aldosterone system (RAAS) is probably the most popular choice, said Dr. Brown of Washington University, St. Louis.

This combination makes physiological sense because the two classes of drugs have complementary modes of action—as the diuretic decreases fluid volume, the RAAS inhibitor decreases pulmonary vascular resistance. RAAS inhibitors also counteract the relative increase in blood pressure from diuretic-induced renin secretion. The combination is well tolerated and effective in low-renin populations and African Americans.

Another popular combination is an ACE inhibitor with a calcium channel blocker (CCB). The ACE inhibitor blocks the renin-angiotensin system, is effective in high-renin hypertension, works in all populations—especially whites, Hispanics, and young patients—and produces arterial and venous vasodilation. The CCB blocks the sympathetic nervous system, provides excellent efficacy, produces arterial vasodilation, is effective in low-renin hypertension, and works in all populations, particularly African Americans and the elderly.

Theoretical considerations suggest that an ACE inhibitor along with an angiotensin II receptor blocker (ARB) should also work, but studies have not shown enhanced blood pressure reduction, although the combination does result in significant reduction in proteinuria.

The combination of a dihydropyridine CCB (such as amlodipine, nifedipine, or isradipine) with a nondihydropyridine CCB,

such as verapamil or diltiazem, may be more effective. The dihydropyridines are less likely to decrease cardiac output and may cause an acute reflux tachycardia. The nondihydropyridines lower the pulse rate and may have a negative inotropic effect. The nondihydropyridines also inhibit the cytochrome P450 system and slow metabolism of the dihydropyridine CCBs. There's good evidence that this combination decreases blood pressure, Dr. Brown said.

Two other treatments for refractory hypertension—insulin sensitizers or statins—

**There is good evidence that the combination of a dihydropyridine CCB with a nondihydropyridine CCB will decrease blood pressure.**

take into account common comorbidities such as dyslipidemia and obesity.

Thiazolidinedione insulin sensitizers can bind to peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) in fat and muscle to lower insulin resistance. Studies have shown such receptors are also plentiful in the kidney, and that two mutations in the PPAR $\gamma$  gene are associated with severe hypertension in humans. Pioglitazone seems to result in significant decreases in systolic blood pressure in clinical trials.

The statins reduce cholesterol, are atheroprotective and stabilize atherosclerotic plaques, have antioxidative effects, reduce inflammation and thrombus formation, and improve endothelial function. A small study has now shown that statins can reduce the magnitude of angiotensin-induced increases in blood pressure.

Nitrates are effective for the acute treatment of severe hypertension and aortic dissection, but long-term use is hampered by tachyphylaxis and tolerance. Some studies have suggested intermittent dosing of long-acting nitrates led to a decrease in the augmentation index of the reflected pulse wave, thus lowering systolic blood pressure.

Dr. Brown has received research support from GlaxoSmithKline and Novartis, is a consultant for Pfizer, and is on speakers' bureaus for five pharmaceutical companies. The meeting was cosponsored by the American Society of Hypertension. ■

# Candesartan Reverses Left Ventricular Hypertrophy in Hypertensives

BY ERIK GOLDMAN  
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MADRID — Antihypertensive therapy with candesartan was shown to reverse left ventricular hypertrophy in a study, Dr. Vivencio Barrios reported at the annual meeting of the European Society of Hypertension.

Findings in several recently published controlled randomized trials have shown that regression of electrocardiographic left ventricular hypertrophy (LVH) improves prognosis of hypertensive patients, “but information on LVH

regression in clinical practice has been scarce,” said Dr. Barrios of the cardiology institute at Ramon y Cajal Hospital, Madrid.

Dr. Barrios was the lead investigator in an open-label, 12-month study evaluating the impact of candesartan, an angiotensin-1 receptor blocker, on LVH in a real-world practice setting. The study involved 276 patients with uncontrolled essential hypertension. The mean blood pressure at baseline was 164/92 mm Hg. The patients' average age was 62 years, and 18% had diabetes.

The researchers assessed LVH

with electrocardiography by using the Cornell voltage duration product (VDP) measurement, as well as QRS-segment duration. The baseline and posttreatment ECG tracings were assessed by a single lab, by a blinded investigator. At the outset of the study, 24% of the patients had LVH.

Patients were treated with candesartan 8 mg/day or 16 mg/day, with the objective of reaching pressures below 140/90 mm Hg for nondiabetics or 130/80 for diabetic patients. The researchers could add other antihypertensive medications if the pressure values

did not drop within target ranges after several months.

At 12 months, the angiotensin-1 receptor blocker produced the expected degree of pressure reduction, decreasing the baseline mean values of 164/92 mm Hg to 143/84 mm Hg. It also produced a significant decrease in the prevalence of LVH. By the end of the study, 20% of the study population had ECG evidence of LVH, down from 24% at the outset. Of those with LVH, 19% showed observable LVH regressions.

On average, the VDP was significantly reduced by 132.88 mm

x msec; the QRS interval was also reduced by 2.95 msec, both indicating a trend away from LVH.

The VDP changes were larger in older patients and in those with higher baseline VDP values, suggesting candesartan offers the greatest potential benefit in those with the most advanced LVH.

Earlier detection and reversal of LVH is of great concern among hypertension specialists who hope that primary care physicians will join them in their efforts to prevent heart failure, for which advanced age and presence of LVH are the top risk factors. ■