Potent BP Lowering

Dual-Acting Drug *from page 1*

24-hour ambulatory monitoring sessions to have daytime pressures of 140-179 mm Hg SBP and less than 110 DBP.

After a washout period of about 1 month, patients were randomized to either 200 mg or 500 mg of PS433540 or placebo and treated for 4 weeks.

Baseline characteristics per arm were similar, including white race in about 80%, mean age of roughly 59 years, mean SBP of about 160 mm Hg, mean DBP of about 94 mm Hg, and mean weight of 90 kg. Efficacy analysis, based on follow-up ambulatory monitoring, was available for 93 subjects.

"At 250 mg, the DARA compound provided similar AT1 receptor blockade as irbesartan 300 mg," he reported. "At 500 mg, we saw the equivalence of 100% AT1 blockade and, we believe, 100% endothelin blockade."

At the highest dose, the mean change from baseline in 24-hour BP was –14.8 mm Hg SBP and –10.1 DBP, compared with –0.4 mm Hg SBP and –0.3 mm Hg DBP with placebo. Both differences were statistically significant. Change in mean seated office BP was –17.3 mm Hg systolic and –9.8 mm Hg diastolic with 500 mg, compared with –4.2 mm Hg systolic and +1.6 mm Hg with placebo, a significant difference. The lower dose of the DARA compound was only slightly less effective. From midnight to 6:00 a.m., when baseline SBP is naturally lower, the mean change was –14 mm Hg SBP, he reported.

"Based on the 'rule of 10,' where each additional antihypertensive produces another 10 mm Hg reduction in SBP, you can see that this is almost twice what we expect with other monotherapies, and close to what we achieve with fixed-dose combinations," Dr. Neutel noted.

PS433540 was well tolerated, with no greater occurrence of adverse events in the active arms and the only serious adverse events and discontinuations occurring with placebo, noted Dr. Neutel, who is on the clinical advisory board of Pharmacopeia, the developer of PS433540 and sponsor of the trial. ■

CPAP Lowers Nocturnal Pressure in Apnea

BY CAROLINE HELWICK
Contributing Writer

NEW ORLEANS — Obstructive sleep apnea appears to contribute importantly to both the development and severity of hypertension and may play a role in heart failure as well. The good news is that regular use of continuous positive airway pressure not only treats the apnea but also lowers blood pressure in some patients, according to speakers at the annual meeting of the American Society of Hypertension.

Obstructive sleep apnea (OSA) has been observed in approximately 40% of persons with treatable hypertension, compared with approximately 25% of men and 10% of women in the general population, according to Dr. David Calhoun of the department of medicine at the University of Alabama at Birmingham.

"A number of studies suggest that nocturnal blood pressure may be a better predictor of cardiovascular outcomes than daytime elevations in blood pressure, so there is growing interest in what is happening during the night, especially when blood pressure fails to decrease. One factor in this is obstructive sleep apnea," Dr. Calhoun said at a press conference on the topic.

Others have found a dose-dependent increased risk of developing hypertension in relationship to OSA. In a prospective evaluation of normotensive patients, those with the most severe OSA at baseline had more than twice the risk of developing hypertension over 4 years (JAMA 2000;283:1829-36).

"This confirmed the relationship between OSA and hypertension, establishing sleep apnea as a potential cause," he said.

Other studies also have found that, the more severe the sleep apnea, the higher a patient's nocturnal and daytime blood pressure, as well. One important study documented the overall prevalence of OSA (defined as more than 10 events per hour) to be 83% among persons with drug-resistant hypertension, including 96% among men and 65% among women.

"You are seemingly at much higher risk of having sleep apnea if you have difficult to control hypertension. And it suggests that having sleep apnea contributes to difficulties in treating hypertension," Dr. Calhoun noted.

OSA also has been associated with heart failure, according to Dr. Alexander G. Logan of Mount Sinai Hospital, Toronto, and the University of Toronto. In the Sleep Heart Health Study (Am. J. Resp. Crit. Care Med. 2001;163:19-25), persons with sleep-disordered breathing had an odds ratio of 2.38 for developing heart failure, as well as an increased risk of stroke and coronary heart disease, versus those without. Numerous other studies have also shown an increased risk of OSA in persons with heart failure, he said.

Treatment of OSA with continuous positive airway pressure (CPAP) may help some patients, a number of studies have shown, the speakers said.

While the data may not be "very compelling," according to Dr. Calhoun, randomized studies have shown that about 5 hours of CPAP per night is associated with small reductions in mean arterial pressure and about 10 mm Hg reduction in systolic and diastolic pressures. In one study of patients with resistant hypertension, regular use of CPAP for 2 months was associated with substantial reductions in 24-hour, daytime, and nocturnal blood pressures (Eur. Respir. J. 2003;21:241-7), a finding that established CPAP as an important adjunct to treatment of patients with resistant hypertension, he said.

"The benefit of CPAP appears to be strongest in nocturnal blood pressures," he added. "CPAP appears to help restore the 'dipping' pattern (10% decrease in blood pressure) overnight."

Dr. Calhoun believes this translates into cardiovascular benefits. French investigators found fewer cardiovascular events among hypertensive patients who adhered to CPAP for 5 years, vs. those patients who discontinued CPAP (Eur. Heart J. 2004;25:728-734). Event rates were 24% vs. 58%, respectively.

Dr. Logan noted that in medically treated heart failure patients with OSA, the use of CPAP reduces systolic blood pressure, partly as a result of a decrease in sympathetic vasoconstrictor tone; improves left ventricular systolic function; improves baroreflex sensitivity; decreases the frequency of ventricular premature beats; and improves the quality of life in hypersomnolent patients. ■

New Anticancer Drugs Often Trigger Serious Hypertension

BY MITCHEL L. ZOLER
Philadelphia Bureau

NEW YORK — Several new and effective anticancer drugs have produced the unexpected and potentially serious side effect of hypertension in many patients.

Drugs that work by inhibiting the vascular endothelial growth factor signaling pathway (VSP), such as bevacizumab (Avastin), sunitinib (Sutent), and sorafenib (Nexavar), all have been documented to trigger hypertension in roughly 10%-40% of patients. In many cases treatment has led to grade 3 hypertension, with BP rising over 180/110 mm Hg, Dr. Michael L. Maitland said at a symposium on cardiovascular disease in cancer patients, sponsored by the University of Texas M.D. Anderson Cancer Center, Houston. In some cases patients also developed heart failure, which was severe in some instances.

Although the magnitude of the problem of hypertension that is triggered by these drugs remains poorly understood, and it is unclear whether BP elevation is necessary to promote their anticancer activity, several rules for their safe use have emerged. First, cancer patients who are candidates for treatment with a VSP inhibitor should undergo a thorough pretreatment risk assessment; second, the BP goal for patients receiving a VSP inhibitor is a maximum of 140/90 mm Hg; third, BP should be measured accurately, early, and often in patients on one of these drugs; and finally, when hypertension develops, it should be promptly treated.

In addition, if a patient's BP spikes, the treatment with the VSP inhibitor should be immediately stopped until the pressure can be normalized, said Dr. Maitland, an oncologist and pharmacologist at the University of Chicago. If the anticancer treatment led to a hypertensive emergency, it should not be restarted.

If blood pressure spikes in a patient taking a VSP inhibitor, the treatment should be immediately stopped until the pressure can be normalized.

A working group of experts are in the process of writing consensus management recommendations for VSP inhibitor-triggered hypertension, Dr. Maitland said in an interview. Until these guidelines are issued, "the starting point is to treat it like conventional hypertension," using agents such as ACE inhibitors, angiotensin-receptor blockers, calcium-channel blockers, and β-blockers, he said.

"Aggressive treatment of blood pressure may substantially minimize the cardiotoxicity" of new anticancer drugs, including sunitinib and imatinib, another anti-cancer drug that's been implicated in causing heart damage, Dr. Aarif Y. Khakoo, a cardiologist at M.D. Anderson Cancer Center in Houston, said in a separate talk at the meeting, which also was sponsored by the American College of Cardiology and the Society of Geriatric Cardiology.

The consequences of a profound spike in BP and possibly other physiological changes caused by drugs like sunitinib have been documented in results from recent studies. A review of 75 patients with metastatic gastrointestinal stromal tumors who were treated with sunitinib for a median of 34 weeks showed that 35 (47%) eventually became hypertensive, (compared with a 6% prevalence at baseline), with several of these patients developing grade 3 hypertension. Eight (11%) of the sunitinib-treated patients had a cardiovascular event, including six with heart failure (8%) and one with a MI. Of the 65 sunitinib-treated patients who underwent LVEF monitoring, 13 (20%) had their LVEF fall below 50% (Lancet, 2007;370:2011-9).

A multivariate analysis of the outcomes identified a history of coronary artery disease as the only significant independent predictor of a cardiovascular event in sunitinib recipients, conferring a 40-fold increased risk of such an event.

In most patients, the declines in left ventricular function rapidly reversed once treatment with sunitinib stopped, said Dr. Ming Hui Chen, a cardiologist at Brigham and Women's Hospital in Boston and a collaborator on this sunitinib study.

In a second review of 224 patients who were treated with sunitinib at M.D. Anderson Cancer Center, 6 patients (3%) developed significant heart failure within 4-44 days after treatment began, according to a recent report from Dr. Khakoo and his associates (Cancer 2008;112:2500-6). Three patients developed New York Heart Association class IV failure, two had class III heart failure, and the sixth patient developed class II heart failure. One patient died because of this adverse effect, which was linked to sunitinib treatment. All six patients also had increased BP, and the effect of the drug did not fully resolve when treatment stopped. ■