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Hypertension Highlights

New Acute Antihypertensive CCB, Alzheimer's Disease, and More

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Abstract

For the first time in 10 years -- since the bad news with acute-acting nifedipine -- a new calcium channel blocker shows efficacy, and safety, for intravenous use in acute hypertensive episodes. Plus following aliskiren, there are several more direct renin inhibitors in late-phase clinical assessment. More evidence that cardiovascular risk factors, specifically hypertension, are also risk factors for Alzheimer's disease, or at least potentiate its progression -- and that antihypertensive drugs (specifically an ARB) may prevent this. Finally, a further confounder for physicians trying to treat high blood pressure: who can you believe about which medicines are being taken?

First New Drug for Acute Hypertension?

Approximately 3 million patients are treated with intravenous antihypertensive agents each year in US hospitals. One of the major risk factors for acute hypertension is having chronic high blood pressure; 1-2 people out of 100 with chronic hypertension have acute elevations of blood pressure that require urgent medical treatment.[1] The investigational antihypertensive drug clevidipine is currently undergoing late-stage clinical development to evaluate its potential as a novel ultrashort acting intravenous treatment for acute hypertension, both in hypertensive emergencies, encountered in the emergency department and intensive care units, as well as perioperative hypertension. The drug has an ultra-short half life of about 1 minute and is characterized by a unique rapid-on and rapid-off pharmacologic profile. If approved, it will be the first new treatment for acute hypertension in more than 10 years.

VELOCITY Trial

New phase III data presented at the 2007 annual meeting of the American College of Chest Physicians held October 20-25, 2007 in Chicago, Illinois, show clevidipine (clevidipine butyrate injectable emulsion) provides rapid, predictable, and safe blood pressure control in patients presenting to the emergency department with acute hypertension.[2] The data come from the EValuation of the Effect of ULtrashOrt-Acting Clevidipine In the Treatment of Patients With Severe HYpertension (VELOCITY) trial, a safety study with the primary objective of determining whether patients presenting through the emergency department with severe hypertension could have their blood pressure lowered in a safe and controlled fashion with an intravenous infusion of clevidipine given continuously for ≥ 18 hours. Secondary objectives in this study included time to reach target blood pressure and hemodynamic measurements.

VELOCITY was an open-label, single-arm multicenter study performed in 126 emergency department patients presenting with acute hypertension (systolic blood pressure [SBP] > 180 mm Hg or diastolic blood pressure [DBP] > 115 mm Hg). For each patient, investigators determined a target SBP range to be achieved within the first 30 minutes of clevidipine infusion. Clevidipine was infused via a peripheral line using a non-weight-based dosing regimen and the infusion was maintained or further titrated after 30 min to achieve the desired long-term (≥ 18 hours) SBP target based on the needs of the individual patient. Oral antihypertensive therapy was begun 1 hour before anticipated cessation of clevidipine.

A total of 117 patients (mean age 53 years, 51% female, 77% black), with mean baseline SBP 203 mm Hg were included in the efficacy analysis. In these patients, target blood pressure levels were reached by a median of 10.9 minutes, with 89% (104 of 117) achieving their target within 30 min. Following initial blood pressure control, clevidipine was infused continuously for a median of 21 hours to maintain blood pressure within target limits. Among patients who received 18 hours of continuous clevidipine therapy, 92% (108 of 117) did not require the addition of other intravenous antihypertensive agents during the 18-hour period.

Onset of the effect with clevidipine was rapid, with mean SBP rapidly decreasing during the titration period: -12 mm Hg (-6%) at 3 minutes, -34 mm Hg (-16.5%) at 15 minutes, and -45 mm Hg (-21%) at 30 minutes. The median time to patients achieving a 15% reduction in SBP was 9.5 min. At 18 hours, the blood pressure reduction was -55 mm Hg (-27%) from baseline. Throughout 18 hours, target SBP was maintained at a steady clevidipine infusion rate. A modest 9 beats per minute increase in heart rate was seen at 30 minutes. After 30 minutes and up to 18 hours, heart rate trended back to baseline. Adverse events were reported in 10% of patients. No hypotensive events were reported.

Joseph Varon, MD (The University of Texas Health Science Center and St. Luke's Episcopal Hospital, Houston), who presented the study results, stressed the importance of the rapid control achieved with clevidipine. "Maintaining target blood pressure can prevent potentially irreversible damage to the brain, heart, kidneys, or blood vessels," he said. "Our finding that continuous infusion of clevidipine for a median of 21 hours maintained the target blood pressure is also important, because some patients require prolonged treatment with an intravenous agent to keep their blood

pressure under control." Dr. Varon added that the findings with clevidipine were also significant given the poor health status of patients in the study. Most (81%) had evidence of end-organ injury, including kidney disease (often requiring dialysis), coronary artery disease, and/or myocardial infarction. In addition, 97% had chronic hypertension, 31% had diabetes, 31% had been previously hospitalized for acute hypertension, and 18% had congestive heart failure.

Further Studies With Clevidipine

The new VELOCITY findings are consistent with data presented by William B. Smith, MD (New Orleans Center for Clinical Research, Knoxville, Tennessee) at the American College of Clinical Pharmacy 2007 Annual Meeting, October 14-17, 2007 in Denver, Colorado. Dr. Smith reported a study that evaluated the pharmacologic and safety profile of a prolonged infusion of clevidipine in 60 adult patients with essential mild-to-moderate hypertension.[3] Treated patients withdrew from their oral antihypertensive medications 8-14 days prior to study drug administration. Patients were allocated to 1 of 5 cohorts: clevidipine 2.0, 4.0, 8.0, or 16.0 mg/hr, or placebo. Clevidipine was administered at an initial infusion rate of 2.0 mg/hr and force titrated by doubling increments every 3 minutes to the respective target dose. The target dose was maintained continuously for 72 hours.

Patients treated with all doses of clevidipine showed a rapid onset of drug effect and maintained the reduced SBP at relatively constant levels for the 72 hours and did not develop tolerance to the drug. When clevidipine butyrate was withdrawn, SBP rapidly returned to baseline, with no rebound hypertension and no drug accumulation. No serious adverse events occurred during the study and clevidipine was safe and well tolerated.

Other data from VELOCITY, presented by W Frank Peacock, MD (The Cleveland Clinic, Ohio) at the Annual Scientific Assembly of the American College of Emergency Physicians, October 8-11, 2007 in Seattle, Washington, showed that 97.5% of patients who received intravenous clevidipine and who were eligible to switch to oral therapy did so successfully -- as defined by achieving their target SBP -- within 6 hours of starting oral therapy.[4]

At the 2007 Annual Meeting of the American Society of Anesthesiologists, October 13-17, 2007 in San Francisco, California, a retrospective analysis of clinical trial safety data was reported showing that improved perioperative blood pressure control with clevidipine in patients undergoing cardiac surgery is strongly associated with a reduced risk of kidney dysfunction within 30 days following the procedure.[5] The data came from 3 safety studies collectively known as the Evaluation of Clevidipine in the Postoperative Treatment of Hypertension Assessing Safety Events (ECLIPSE) studies. The main results of these studies were presented at earlier in the year at the American College of Cardiology meeting on March 24-27, 2007 in New Orleans, Louisiana.[6]

The new analysis included a total of 1512 cardiac surgery patients enrolled in 1 of 3 randomized, open-label studies that compared clevidipine with 1 of 3 current intravenous antihypertensive agents: nitroglycerin, sodium nitroprusside, or nicardipine. In these studies, investigators monitored each patient's blood pressure beginning just before the patient went into cardiac surgery, and administered the assigned antihypertensive agent, at their discretion, if the pressure became too high. The dose of antihypertensive agent was adjusted as necessary to achieve the desired response over a 24-hour

period. The magnitude and duration of SBP excursions above or below predefined perioperative SBP ranges (85-145 mm Hg preoperatively and postoperatively, and 75-135 mm Hg during surgery) were calculated for each patient.

The analysis, reported by Solomon Aronson, MD (Duke University Medical Center, Durham, North Carolina), showed a statistically significant association between blood pressure excursions and kidney dysfunction (defined by creatinine being above 2.0 mg/dL, with minimum increase of 0.7 mg/dL) at 30 days. Specifically, the risk of kidney dysfunction was more than 75% in patients with the worst blood pressure control -- those in the top 25% of blood pressure excursions (odds ratio 1.785, confidence interval 1.132-2.815, *P* = .0126). The findings are consistent with others reported from a separate retrospective analysis of ECLIPSE data showing that poor blood pressure control is associated with greater 30-day mortality risk.[7]

Marketing Information

The company developing clevidipine (*Cleviprex*), The Medicines Company, filed a New Drug Application (NDA) for the drug for the treatment for acute hypertension in 2007 and announced its acceptance by the FDA in September.[8] The Medicines Company licensed clevidipine from AstraZeneca in 2002 and has rights to development, licensing, and commercialization of clevidipine worldwide.

More New Direct Renin Inhibitors in Clinical Trials

A new direct renin inhibitor has been entered into clinical trials by the same company that carried out early clinical development of aliskiren, the first renin inhibitor to be approved for the treatment of hypertension in the United States and Europe. Speedel (Basel, Switzerland and Bridgewater, New Jersey) has announced that a phase I trial has begun with SPP676, a compound selected from the SPP600 series of renin inhibitors being developed by Speedel's late-stage research unit for the treatment of hypertension and related end-organ diseases.[9]

The phase I trial of SPP676 is a double-blind, randomized, placebo-controlled study in healthy male volunteers designed to evaluate clinical safety and tolerability following single and multiple oral doses. In addition, the pharmacokinetics and pharmacodynamics of the compound will be assessed. Testing of the single doses has started in October 2007, and the multiple-dose phase of the study is planned to start in 2008. The first results are expected in 2008.

SPP676 is the third proprietary renin inhibitor developed by the company in-house to enter clinical trials, following SPP1148 which entered phase I in Q1 2007 and SPP635 which recently progressed into phase lla. SPP635 is the most advanced compound of the SPP600 series of renin inhibitors.

In June 2007, Speedel reported phase IIa results with SPP635 in hypertensive patients.[10] The trial had a double-blind, placebo-controlled, randomized, parallel design and it evaluated patients treated with a single dosage level of SPP635 once-daily for 4 weeks. It studied the safety and efficacy of SPP635 in 35 male and female patients (20 patients receiving SPP635 and 15 receiving placebo)

with mild-to-moderate hypertension by measuring office and ambulatory blood pressure. SPP635 was safe and well tolerated over the 4-week period, with no serious adverse events reported or any clinically significant changes in laboratory safety parameters. Sitting SBP and DBP measured at trough (24 hours after drug) were significantly reduced, by about 18 and 10 mm Hg, respectively, vs baseline after 4 weeks ($P < .001$), whereas the placebo group remained unchanged. Similar results were observed for ambulatory blood pressure, which was reduced during the day as well as in the night.

Along with previous data showing the half-life of SPP635 to be approximately 24 hours, the ambulatory blood pressure data support the use as of SPP635 as a once-a-day drug. The extent of blood pressure reduction is similar to that reported for aliskiren. Another phase II trial with SPP635 has begun in patients with type 2 diabetes and mild-to-moderate hypertension.[11] The proof-of-concept phase IIa trial will be carried out in Europe with first results expected in the second half of 2008. It will study the safety, tolerability, and efficacy of 2 different doses of SPP635 for 4 weeks in about 50 patients.

Speedel's first renin inhibitor aliskiren (SPP100) was approved to treat hypertension by the US Food and Drug Administration (FDA) in March 2007, and by the European Medicines Agency (EMEA) in August 2007, and is marketed by Novartis in both these regions. Recent results of a phase III clinical trial with aliskiren in diabetic patients, the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) were presented at the American Society of Nephrology's Renal Week meeting in San Francisco.[12] Hans-Henrik Parving, MD (Righospitalet, Copenhagen, Denmark), reported that aliskiren further lowered proteinuria, independent of blood pressure, in diabetic patients already receiving recommended treatment with losartan and optimal antihypertensive therapy. The AVOID study was supported by Novartis.

Another new renin inhibitor, developed jointly by Actelion and Merck has entered phase II clinical trials, according to an announcement by the 2 companies.[13] This follows 4 years of work on renin inhibition in cardiovascular disease, the companies said. Actelion and Merck formed an exclusive worldwide alliance in December 2003 to discover, develop, and market new classes of orally available renin inhibitors for patients suffering from cardio-renal diseases. The 2 companies are jointly funding phase II development, with Merck responsible for funding all phase III and outcome studies. Merck will lead and fund commercialization. Actelion retains a worldwide option to co-promote any product resulting from this alliance as a paid-for sales force.

Blood Pressure and Alzheimer's Disease

Hypertension and Faster Progression of Alzheimer's Disease

Alzheimer's disease (AD) may progress more rapidly in people with hypertension, atrial fibrillation, or angina, according to results of a recent US study published in the November 6 issue of *Neurology*.[14] The findings suggest that these conditions may be modifiable risk factors for secondary prevention in AD, says lead investigator, Michelle M. Mielke, PhD (The Johns Hopkins University School of Medicine, Baltimore, Maryland).

Prior to this study, which was supported in part by the National Institute of Aging, there was considerable epidemiologic evidence that cardiovascular risk factors increase risk of incident AD, but few studies had examined their effect on progression of AD once the diagnosis had been established.

To examine the effect of vascular factors and age on rate of progression in a longitudinal study of incident dementia, Dr. Mielke and co-investigators followed 135 individuals with incident AD who were participating in the Dementia Progression Study as part of the ongoing, population-based Cache County Study on Memory, Health, and Aging, which has been following a group of 5092 Cache County, Utah, residents aged ≥ 65 years since 1995. The participants in Dr. Mielke's study were mostly white women with mild dementia severity (mean Global Clinical Dementia Rating [CDR] score = 1.0). They were followed with in-home visits for a mean of 3.0 years (range: 0.8 to 9.5) and 2.1 follow-up visits (range: 1 to 5). The CDR Scale and Mini-Mental State Examination (MMSE) were administered at each visit, and baseline vascular factors were determined by interview and physical examination.

Both systolic hypertension and atrial fibrillation have previously been reported as risk factors for incident dementia and AD. In this study, multivariate analyses, controlling for demographic and other vascular variables, revealed that the 10 (7.4%) patients who had systolic hypertension (SBP > 160 mm Hg) at the time of diagnosis had approximately 100% faster annual rates of decline on both the CDR and MMSE scores than those with normal blood pressure. In another 10 (7.4%) patients with atrial fibrillation at the time of the diagnosis, the rate of decline was 75% faster than those without atrial fibrillation.

The next question would be whether these results can be affected by therapeutic interventions. A history of coronary artery bypass graft (CABG) surgery, diabetes mellitus, and use of antihypertensive medications at baseline were associated with a slower rate of decline. Use of antihypertensive medications was previously reported to reduce the risk of onset of AD in the Cache County Study.[15] However, the researchers was surprised by the finding with CABG because previous studies, including 1 from the Cache County Study,[16] had reported an association between CABG and cognitive impairment and dementia.

There was an interaction between age and vascular factors in predicting rate of decline, such that SBP ≥ 160 mm Hg, angina, myocardial infarction, and older age were associated with faster decline. "Clearly, these risk factors need to be addressed at younger ages before the onset of cognitive impairment," the authors say. "Future research is needed in this area because determination of age-specific risk factors in important in defining the patient population in which intervention may lead to effective secondary prevention of AD."

In a press release issued by the American Academy of Neurology,[17] Dr. Mielke said that she is currently working on similar studies using larger sample sizes to better understand the potential role that vascular factors play before diagnosis of AD and their role over the course of the disease's progression. Dr. Mielke also recently contributed to a study that examined drugs that modify high blood pressure and high cholesterol, such as beta-blockers, diuretics, calcium channel blockers, and statins, and their effects on cognitive and functional decline. Results from that study are expected to

be released this year.

Blood Pressure Drugs May Prevent Alzheimer's Disease

The Cade County Study of antihypertensive medication use and incident AD mentioned above[15] is part of the evidence that has accumulated about the influence of antihypertensive drugs on the incidence and pathogenesis of the disease. This evidence is inconsistent, however, which was the motivation for a study by researchers at Mount Sinai School of Medicine (New York, NY) to try to resolve some of these inconsistencies. In the November issue of *The Journal of Clinical Investigation*, lead author Jun Wang, PhD, and colleagues report results suggesting that certain antihypertensive drugs influence AD through mechanisms affecting beta-amyloid protein (Abeta), the principal component of plaques that form in the brains of AD patients, independent of blood pressure-lowering activity.[18]

Over the past 2 years, Dr. Wang and her colleagues have screened more than 1500 drugs that are already commercially available for treatment of other disorders, to determine their potential value in treating AD and cognitive impairment. They screened 55 antihypertensive drugs for AD-modifying activity using primary cortico-hippocampal neuron cultures generated from the Tg2576 mouse model of AD. These agents represent all drug classes used for hypertension pharmacotherapy, including alpha-blockers, beta-blockers, alpha-beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers, diuretics, and drugs with other mechanisms of action.

Seven candidate antihypertensive agents were identified that significantly reduced AD-type Abeta accumulation: propranolol, carvedilol, valsartan, losartan, nicardipine, amiloride, and hydralazine. Using an in vitro assay, only 1, the ARB valsartan, was found to be capable of attenuating oligomerization of Abeta peptides into high-molecular-weight oligomeric peptides, known to be involved in cognitive deterioration.

In Vivo Results With Valsartan in Alzheimer's Disease

To follow up on the in vitro results with the ARB, in vivo experiments were carried out in Tg2576 mice treated over 5 months with valsartan 10 or 40 mg/kg/day, which correspond to human doses of 55 and 220 mg/kg/day (which are, respectively, 2-fold below and within the recommended human equivalent therapeutic range). Neither dose of valsartan produced significant changes in SBP, DBP, or mean arterial pressure in these normotensive mice. However, both doses were shown to block the development of Abeta-mediated cognitive deterioration. Untreated mice showed impaired acquisition of spatial learning, as assessed by the Morris water maze test in which they were exposed to visual clues to help locate a submerged escape platform.

After treatment with valsartan, the mice were able to locate the escape platform, and this was dose-dependent, as mice treated with the higher dose performed significantly better than untreated mice. Treatment with the 2 doses also significantly promoted spatial memory retention. The same treatment in strain-, age-, and sex-matched wild-type mice failed to affect spatial reference memory performance compared with untreated control wild-type mice, showing that valsartan may benefit

these deficits in Tg2576 mice selectively, through the attenuation of AD-type Abeta-mediated response in the brain. Attenuation of spatial reference memory deterioration in the Tg2576 mice coincided with an approximately 3-fold reduction in high molecular weight Abeta peptide content in the brain.

From the results of the study, the researchers suggest that valsartan treatment might prevent Abeta-related spatial memory reference deficits in the Tg2576 AD mouse model through a combination of multiple mechanisms, consisting of (a) reducing Abeta aggregation into high molecular Abeta species; (b) increasing Abeta degradation by IDE; and possibly (c) promoting sinking of Abeta peptides from the brain to the periphery.

Cautious Note on Implications

Dr. Wang and her colleagues are currently evaluating the remaining 6 antihypertensive drugs individually for their in vivo efficacy to protect against progressive Abeta neuropathology and Abeta-related memory deficits in AD. Since many factors, including biologic availability and drug metabolism, may influence Abeta-lowering activity of a drug in vivo, some drugs that are biologically active in vitro may not be effective in vivo, the researchers point out. Thus, individual drugs must be investigated on a case-by-case basis.

In a press release issued by Mount Sinai School of Medicine, lead investigator Giulio M. Pasinetti, MD, PhD stressed that further studies are needed on humans to see whether these antihypertensive agents might have the same effect they had in mice.[19] "The use of these drugs for their potential anti-Alzheimer's disease role is still highly experimental, and at this stage we have no clinical data beyond phenomenological observation in humans" said Dr. Pasinetti. "We need to complete preventive and therapeutic clinical trials in the near future if we are to identify certain antihypertensive drugs with anti-beta-amyloid antioligomeric activities, which will need to be prescribed at dosages that do not interfere with blood pressure in normotensive Alzheimer disease patients."

Patients Often Unable to Remember Which, and How Many, Antihypertensive Medications They Are Taking

A study funded by the Agency for Healthcare Research and Quality, the Centers for Disease Control and Prevention (CDC) and the Michigan Department of Community Health has found that patients taking antihypertensive drugs frequently could not name which medications they were taking, and there was little agreement between the drugs listed in the medical records and those named by patients. In fact, almost 50% of the patients were unable to accurately name a single 1 of the drugs listed in their medical chart.

This problem is known as "health literacy." Health literacy is defined in *Healthy People 2010* as: "The degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions."[20] This involves the ability to understand instructions on prescription drug bottles, appointment slips, medical education brochures, doctor's directions and consent forms, and the ability to negotiate complex health care systems.

Health literacy varies by context and setting and is not necessarily related to years of education or general reading ability. Patients with limited health literacy have been shown to have a poorer understanding of prescription medicine names, indications for use, and instructions.

For this study, reported in the November issue of the *Journal of General Internal Medicine*,[21] Stephen D. Persell, MD, MPH, and colleagues interviewed 119 patients aged 18 years or older who had a diagnosis of hypertension and attended an appointment at 1 of 3 primary care clinics in Grand Rapids, Michigan, between July 2005 and March 2006. All patients were English speaking and were deemed physically and cognitively able to participate in the study. A large proportion of patients were women (69.5%), black (60.5%), had less than a high-school education (39.0%), and 45.5% had annual household incomes < $10,000.

Functional health literacy was assessed in these subjects using the short form of the Test of Functional Health Literacy in Adults (S-TOPHLA), a practical measure of functional health literacy with good reliability and validity that can be used by health educators to identify individuals who require special assistance to achieve learning goals.[22] The test takes up to 12 minutes to administer. In addition, patients were asked to name the different antihypertensive medications they were taking. These were compared with the drugs listed in each patient's medical record.

Only 22.7% of the patients could name ≥ 2 of the antihypertensive medications and 40.3% could not name any. Of the 119 patients interviewed, just over 30% were found to have inadequate health literacy, according to the S-TOPHLA, and these patients tended to be older, have completed fewer years of schooling, and were more likely to be prescribed ≥ 2 antihypertensive medications. Patients with inadequate health literacy were less able to name any of their antihypertensive medications compared with those with adequate health literacy (40.5% vs 68.3%, $P = .005$), and this relationship remained unchanged after further adjustment for race and years of education. Agreement between patient reported medications and the medical record was also lower in patients with inadequate health literacy, with 65% vs 38% of health literate and unliterate patients, respectively, able to report no medications in common with their medical record lists.

Worse Than Expected

Commenting on the study, Dr. Persell admitted that the findings were worse than he and his colleagues had expected. He stressed the importance of patients being able to tell physicians outside their usual source of care, such as those in emergency departments or inpatient settings. "Poor reconciliation may further complicate the challenge of coordination of care," he noted. "We think doctors may be prescribing more medications because the patients aren't giving them the right information about what they are taking," he said.

Needless to say, this lack of "health literacy," leading to lack of correct medication information, compounds the challenge for physicians trying to titrate or change medications or monitor nonadherence (this is called "medical reconciliation"). Dr. Persell suggested that perhaps the solution should be to encourage patients to bring all their current medicine bottles with them for office visits, so that the physician can compare them to what has actually been prescribed in the medical charts.

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