maintaining normal bioavailable levels of the vasodilator and anti-remodeling molecule nitric oxide. Together, these observations raised the possibility that coupling the mineralocorticoid-receptor antagonist spironolactone with therapies that inhibit the adverse effects of ET_A-mediated pulmonary vasoconstriction/remodeling may be a useful therapeutic strategy for patients with PAH.

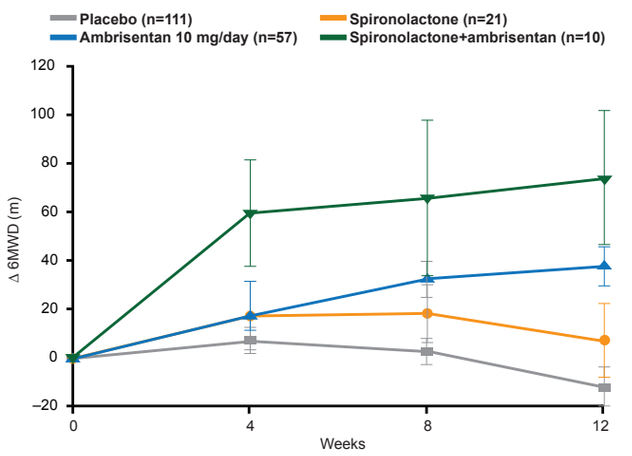
This study analyzed data from patients in the double-blind, placebo-controlled Ambrisentan in Patients With Moderate to Severe Pulmonary Arterial Hypertension studies [ARIES-1 and -2; Galiè N et al. *Circulation* 2008] who were randomized to receive placebo or the selective ET_A antagonist ambrisentan (10 mg daily) and in whom spironolactone use was reported. The investigators elected to study patients randomized to the maximum dose of ambrisentan because it was at this dose that the greatest benefit on clinical outcome was observed in the ARIES trial. Critiera for inclusion in the spironolactone treatment group was as follows: study drug use for ≥28 days, initiation of spironolactone prior to enrollment or ≤28 days after first ARIES study drug day, and discontinuation of spironolactone >28 days prior to the final ARIES study drug dose. Twenty-one patients in the placebo group (21/132; 15.9%) and 10 patients in the ambrisentan group (10/67; 14.9%) met the spironolactone criteria.

Patients treated with ambrisentan plus spironolactone tended to have increased mean pulmonary vascular resistance (14.5±6.0 vs 10.8±5.7 Wood units; p=0.07) and plasma B-type natriuretic peptide (BNP) concentrations (236.7 ng/L; 95% CI, 81.5 to 687.4 vs 131.7 ng/L; 95% CI, 88.0 to 197.2; p=0.24) compared with those treated with ambrisentan alone.

On the primary endpoint of change from baseline in 6-minute walk distance at Week 12, patients treated with ambrisentan plus spironolactone achieved a mean peak mean change of +74.2 meters compared with +38.2 meters for those treated with ambrisentan alone (p=0.11; Figure 1).

A similar trend was observed for the predetermined secondary endpoints: ambrisentan plus spironolactone was associated with a 1.7-fold improvement in BNP levels (p=0.08) compared with ambrisentan alone at Week 12 and a decrease in the geometric BNP mean of 66% compared with 39% decrease for ambrisentan alone at Week 12. World Health Organization functional status improved by ≥1 class in 50.0% of patients treated with ambrisentan plus spironolactone versus 21.6% of placebo-treated patients (p=0.01). Additionally, none of the patients treated with ambrisentan plus spironolactone reached the clinical endpoints of progressive illness, PAH-associated hospitalizations, and/or death versus 5.3% of patients treated with ambrisentan only.

Figure 1. Change From Baseline in the 6-Minute Walk Distance



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Limitations of the study include the retrospective design and small sample size. In addition, aldosterone levels were not measured in the ARIES trial nor were potential mechanisms by which aldosterone influenced outcomes. Additionally, the investigators recognized that use of spironolactone may be a marker of more severe PAH and that the clinical response observed in patients treated with ambrisentan plus spironolactone reflects the enhanced therapeutic efficacy of ambrisentan. Nevertheless, these results support the hypothesis that spironolactone and ET_A antagonism may be beneficial in PAH, and, overall, results from this study provide evidence to support future clinical trials to characterize the efficacy of aldosterone inhibition in the treatment of PAH.

Haloperidol Does Not Prevent Delirium in Ventilated ICU Patients

Written by Emma Hitt, PhD

Treatment of ventilated patients in the intensive care unit (ICU) with haloperidol or intravenous saline resulted in similar rates of delirium- and coma-free days. Valerie Page, MB, BCh, Wirral University Teaching Hospital NHS Foundation Trust, Wirral, United Kingdom, presented data from the Randomised, Double-Blind, Placebo-Controlled Trial to Compare the Early Administration of Intravenous Haloperidol Versus Placebo in the Prevention and Treatment of Delirium in Critically Ill Ventilated Patients [HOPE-ICU; ISRCTN83567338].

Between 55% and 80% of ventilated ICU patients have delirium, with an estimated 65% unrecognized or untreated. Although limited evidence supports the use of haloperidol in delirium in critical patients, a survey of practitioners in the United Kingdom demonstrated that up to 95% and 80% of practitioners use haloperidol to treat hyperactive delirium and hypoactive delirium, respectively. The HOPE-ICU trial tested the hypothesis that early treatment of critically ill patients with haloperidol will increase the number of days alive without delirium or coma.

In the single-center, Phase 2, double-blind, placebo-controlled HOPE-ICU trial, 142 patients were randomized 1:1 to receive haloperidol 2.5 mg or intravenous saline every 8 hours for up to 14 days, at discharge, or until patient was delirium-free for 2 consecutive days. Patients were included if they required ventilation within 72 hours of ICU admission and were excluded for chronic antipsychotic use, Parkinson's disease, a QTC of greater than 500 msec, uncomplicated elective heart surgery, dementia, likelihood to leave or die within 48 hours, pregnancy, or readmission. Patients were assessed daily for delirium by the confusion assessment method-ICU.

The primary endpoint of the HOPE-ICU trial was the number of days alive free of delirium or coma at 14 days. The number of ventilator-free days at Day 14, delirium-free, coma-free, and mortality at 28 days, length of critical care, and length of hospital stay were considered secondary endpoints.

No significant difference was observed in delirium-free or coma-free days at Day 14 between patients that were treated with haloperidol or placebo. The trend of nonsignificance continued to Day 28. In addition, there was no significant difference between the haloperidol or placebo arms in the secondary endpoints of number of ventilator-free days at Day 14, delirium-free days and mortality at Day 28, length of ICU stay, and length of hospital stay.

The safety profiles were similar among the haloperidol and placebo arms. A QTC of >500 msec after electrolyte correction occurred in seven patients in the haloperidol arm and four patients in the placebo arm (p=0.29). Oversedation despite decreasing the dose by half occurred in eight patients in the haloperidol arm and five patients in the placebo arm (p=0.35). Extrapyramidal symptoms were not observed among patients in the haloperidol arm (after halving the dose) and in one patient in the placebo arm (p=0.57).

The data from HOPE-ICU indicates that treatment of ventilated ICU patients with haloperidol does not prevent or treat delirium. Prof. Page said that, in ICU patients with delirium, perhaps the target pathophysiology is actually neuroinflammation, rather than neurotransmitter imbalance.

Beraprost Plus Sildenafil Effective in Pulmonary Arterial Hypertension

Written by **Emma Hitt, PhD**

Combination treatment of beraprost and sildenafil results in improved 6-minute walk test (6MWT) distance and decreases N-terminal pro-brain natriuretic peptide (NT-proBNP) levels and time to worsening in patients with pulmonary arterial hypertension (PAH). Zhi-Cheng Jing, MD, Fu Wai Hospital & National Center for Cardiovascular Disease, Beijing, China, presented data from the Beraprost Combined Therapy With Sildenafil for Pulmonary Arterial Hypertension study [BEST; ChiCTR-TCC-12002776].

Patients with PAH have poor long-term survival rates, highlighting a need for a first-line combination therapy. This is particularly important in China, where many novel targeted agents for the treatment of PAH are not available in typical daily practice. The hypothesis of the BEST study was that the addition of beraprost to sildenafil would improve efficacy in the treatment of PAH.

In the open-label BEST study, 60 patients with PAH receiving sildenafil monotherapy were randomized to receive beraprost in addition to sildenafil, or continue with sildenafil monotherapy. Patients aged 18 to 65 years who had World Health Organization functional class (WHO-FC) II to IV symptomatic PAH and a 6MWT of 150 to 450 meters at baseline who were receiving sildenafil monotherapy for 3 to 6 months were included in the study.

Follow-up at 12 weeks and 24 weeks included a 6MWT, WHO-FC assessment, and NT-proBNP analysis. The primary endpoint was improvement in the distance of the 6MWT. WHO-FC, NT-proBNP levels, hemodynamic parameters, and time to clinical worsening were the secondary endpoints.

At 12 weeks, patients treated with combination therapy demonstrated a mean 6MWT distance increase of 43.6 meters, as compared with 7.4 meters in the sildenafil monotherapy group (p=0.072). At 24 weeks, patients that received combination therapy had a mean 6MWT distance increase of 50.8 meters, as compared with 5.6 meters in the monotherapy arm (p=0.04).

A significant decrease in NT-proBNP levels was observed in the combination-therapy arm of 437 pg/mL at Week 12 and 399 pg/mL at Week 24, as compared with a 300-pg/mL increase at Week 12 (p<0.001) and a 46-pg/mL increase at Week 24 in the monotherapy arm (p<0.001). In addition, significantly more patients in the combination arm improved WHO-FC by at least one class, as compared with patients in the monotherapy arm (p=0.01). Event-free survival was significantly greater in the beraprost plus sildenafil group, as compared with the sildenafil monotherapy group (p=0.027).