

Pulmonary Vascular: Pulmonary Hypertension, continued

months following combination therapy was significantly higher than the first baseline by 68 meters.

CONCLUSION: These results show that, in patients who do not achieve a satisfactory improvement in exercise tolerance with monotherapy, initiating combination therapy (even after approximately 1 year of monotherapy treatment) may result in further improvement in exercise tolerance. Randomized controlled studies with a large number of patients are needed to address the benefit (improved quality of life and survival) of combination therapy in this group of patients.

CLINICAL IMPLICATIONS: Early initiation of combination therapy may prove beneficial in improving exercise tolerance and survival in patients with PAH.

DISCLOSURE: Hassan Al-Sharif, None.

ROLE OF ENDOTHELIN RECEPTOR ANTAGONIST IN PULMONARY HYPERTENSION ASSOCIATED WITH DIET PILLS AND/OR STIMULANTS

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PURPOSE: Endothelin-1 is a potent vasoconstrictor and smooth-muscle mitogen. Many studies have shown that orally administered dual endothelin-receptor antagonist bosentan improves exercise capacity and cardiopulmonary hemodynamics in some patients with pulmonary arterial hypertension. These studies have not included patients with pulmonary hypertension secondary to diet pills or stimulants. The present study investigates the effect of bosentan on exercise capacity specifically in patients with pulmonary hypertension who have consumed diet pills or stimulants.

METHODS: Case control matched study comparing patients with pulmonary hypertension exposed to diet pills and/or stimulant (n=23) treated with bosentan to patients with pulmonary hypertension not exposed to anorexigens and/or stimulants (n=25) chosen from pulmonary hypertension database between 1995 and 2005. The primary end point is the change in exercise capacity before and after treatment with bosentan between these two groups.

RESULTS: Patients with pulmonary hypertension who were exposed to diet pills and/or stimulants had poor baseline exercise capacity compared to patients who were not exposed to diet pills and/or stimulants (P = 0.03). At week 12, patients with pulmonary hypertension associated with diet pills and/or stimulants treated with bosentan had an increase in 6-minute walking distance by 172 feet (SD ± 353) compared to patients not exposed to diet pills and/or stimulants with an increase by 31 feet (SD ± 197); P = 0.16.

CONCLUSION: There was a definitive positive effect on exercise capacity in patients with pulmonary hypertension treated with bosentan both exposed and not exposed to diet pills and/or stimulants. However, there was better response to bosentan in their exercise capacity in patients exposed to diet pills and/or stimulants, potentially because they were sicker at baseline and had a significant effect on treatment. More studies are required to understand their pathophysiology in treating these patients with bosentan.

CLINICAL IMPLICATIONS: Endothelin receptor antagonist may be considered for treatment of patients with pulmonary hypertension exposed to diet pills and/or stimulants.

DISCLOSURE: Uma Mohanasundaram, None.

AMBRISANTAN HAS NO CLINICALLY RELEVANT EFFECT ON THE PHARMACOKINETICS OR PHARMACODYNAMICS OF WARFARIN

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PURPOSE: Ambrisentan is a high affinity, propanoic acid-class, ETA-selective endothelin receptor antagonist (ERA). Ambrisentan doses of 2.5 and 5 mg once-daily have been shown to improve 6-minute walk distance and delay clinical worsening in a placebo-controlled study (ARIES-2) of patients with pulmonary arterial hypertension (PAH), with no incidence of serum aminotransferases >3xULN. Warfarin anticoagulation therapy is common for patients with PAH. When coadministered, sulfonamide-class ERAs have been shown to induce (bosentan) or inhibit (sitaxsentan) the p450-dependent metabolism of warfarin and alter the pharmacokinetic (PK) and pharmacodynamic (PD) effects of warfarin. Therefore, the

potential for ambrisentan to affect the PK or PD of warfarin was examined.

METHODS: 22 healthy adults received a 25 mg dose of racemic warfarin alone and after 8 days of ambrisentan 10 mg qd. R- and S-warfarin plasma concentrations were measured over a 96-hour period and exposure (AUC_{0-last}) and maximum plasma concentration (C_{max}) were determined. Prothrombin time was measured over a 96-hour period and cumulative prothrombin time (PTAUC) and maximum prothrombin time (PT_{max}) were assessed.

RESULTS: Slight increases in AUC_{0-last} were observed for R- and S-warfarin after 8 days of ambrisentan administration (+4.7% [90% CI: +1.7% to +7.7%] and +1.9% [90% CI: -1.4% to +5.3%], respectively), whereas, C_{max} for R- and S-warfarin were decreased (-8.4% [90% CI: -13.8% to -2.6%] and -10.1% [90% CI: -15.2% to -4.7%], respectively). The PTAUC and PT_{max} associated with warfarin administration were decreased slightly with concomitant ambrisentan administration (-6.6% [95% CI: -8.7% to -4.6%] and -14.2% [95% CI: -16.6 to -11.8], respectively). Confidence intervals for all PK and PD parameters were within the pre-specified equivalence criteria.

CONCLUSION: Ambrisentan administration had little effect on the AUC_{0-last} or C_{max} of R- or S-warfarin. A slight reduction in prothrombin time was observed for a single-dose of warfarin following ambrisentan administration. However, based on confidence intervals, all changes in warfarin PK and PD were not considered to be clinically relevant.

CLINICAL IMPLICATIONS: Dosage adjustment for warfarin therapy should not be required with concomitant ambrisentan administration.

DISCLOSURE: Michael Gerber, Employee Myogen, Inc.; Product/procedure/technique that is considered research and is NOT yet approved for any purpose, ambrisentan.

TREATMENT OF PORTOPULMONARY HYPERTENSION: EXPERIENCE WITH SILDENAFIL

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PURPOSE: The prevalence of portopulmonary hypertension (PPHTN) in patients with end stage liver disease is 3.5% to 12.5%. Elevated pulmonary arterial pressures is associated with significant morbidity and mortality and may preclude patients from receiving liver transplantation. The purpose of this study was to observe the effects of Sildenafil therapy on symptoms, pulmonary hemodynamics, and exercise tolerance in patients with PPHTN.

METHODS: We retrospectively reviewed the medical records of 10 patients with PPHTN treated with Sildenafil, at 3 centers, from 2001-2005. Study variables included patient demographics, symptoms, WHO class, pulmonary hemodynamics, and six minute walk test results (6MWT). For all continuous variables we report means ±SD and use frequencies to describe categorical data. We use the Wilcoxon test to compare differences in continuous variables before and after treatment of PPHTN. A two tailed p <0.05 is considered statistically significant for all analyses.

RESULTS: 70% of patients were female with a mean age of 55 ± 10 years. Prior to treatment, 90% of patients reported dyspnea with activity, 60% had fatigue, one patient was WHO class 4, 6 were class 3, 2 were class 2 and only 1 was class 1. Mean RVSP was 66 ± 21 mmHg, mPAP 49 ± 15 mmHg, and PVR 812 ± 502 dynes.sec/cm⁵. The mean 6MWT, available for 5 patients was 319 ± 196 m. Patients received a mean dose of 155 ± 75 mg/day of Sildenafil for an average of 152 days prior to repeat measurements. Post treatment, there was improvement in symptoms with 60% of patients WHO class 2 and 40% WHO class 1. Although there was no statistically significant difference in pulmonary hemodynamics and 6MWT, pre and post therapy, there was a trend towards reduction of mPAP and PVR and improvement in 6MWT.

CONCLUSION: Sildenafil was associated with symptomatic improvement in PPHTN and a trend towards decrease in mPAP.

CLINICAL IMPLICATIONS: Sildenafil is effective in reducing symptoms of PPHTN. Prospective studies are needed to further explore these results.

DISCLOSURE: Orlando Rodriguez, None.