Efficacy of Endothelin Receptor Antagonists in Pulmonary Arterial Hypertension Patients With and Without History of Exposure to Anorexigens and Stimulants

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Abstract

Objective: To compare the effectiveness of endothelin receptor antagonists (ERAs) in Pulmonary Arterial Hypertension (PAH) patients with and without exposure to anorexigens and/or stimulants as measured by six-minute walk test (6MWT), New York Heart Association (NYHA) functional class and clinical outcomes.

Methods: This is a retrospective case-control analysis of PAH patients with (n=20) and without exposure (n=20) to anorexigens and/or stimulants who were treated with the ERA bosentan for 3 months. The primary end point was change in exercise capacity as assessed by 6MWT; NYHA classification and clinical events (death or transplantation) were also assessed.

Results: PAH patients with a history of exposure to anorexigens and/or stimulants had poorer baseline exercise capacity compared to patients who did not have a history of exposure (P = 0.03). After 3 months treatment with an ERA (bosentan) patients with a history of anorexigen and/or stimulant exposure had an increase in 6MWT of 63 meters (SEM ± 17), while unexposed patients had an increase of only 16 meters (SEM ± 23) (p=0.11). In the group of patients with exposure more patients improved NYHA functional class with ERA treatment but there were more patients with adverse clinical outcomes (2 deaths, 2 lung transplants).

Conclusion: Bosentan improved exercise capacity in PAH patients regardless of exposure to anorexigens and/or stimulants but the greatest improvement in 6MWT and NYHA class was in patients with a history of exposure. Patients with an exposure history, however, had more adverse clinical outcomes despite these improvements in 6MWT and NYHA.

Introduction

Pulmonary arterial hypertension (PAH) is an indolent, debilitating vascular disease characterized by an increase in pulmonary vascular resistance leading to right ventricular failure and death [1].

A relationship between diet pills and PAH was first observed in the 1960s following an epidemic of PAH which occurred after the release of the anorexigen, Aminorex in Europe[2]. Subsequently in the 1990s an association was established between use of the anorexigen, fenfluramine, and PAH [3]. Patients with PAH due to exposure to fenfluramines appear to be comparable to patients with idiopathic PAH (IPAH) with respect to symptoms, clinical features, and hemodynamics but have lower survival rates when compared to patients with IPAH (1-year survival 50% vs. 88% and 3-year survival 17% vs. 60%)[3]. Methamphetamine abuse is a recognized risk factor for PAH and patients with a history of exposure to these stimulants may represent a growing population of patients with PAH. From 1984 to 1993, methamphetamine use in California rose by 366%. In some regions of California, methamphetamine-related morbidity increased over 1000% during this 10-year period [4].

It is unclear which factors may predict a good response to specific treatments in patients with PAH, and whether or not that response will translate into improved clinical outcomes. In previous studies bosentan improved exercise capacity, NYHA class and clinical events in patients with PAH[5]. It is unclear if ERAs can or should be expected to have similar effects in patients with PAH due to anorexigen and/or stimulant exposure as these patients were never specifically studied. We undertook this study to attempt to answer that question.

Objective

To compare the effects of bosentan in PAH patients with and without exposure to anorexigens and/or stimulants as assessed by 6 minute walk test, NYHA functional class and clinical outcomes.

Methods & Materials

- A cohort of patients diagnosed with pulmonary arterial hypertension between 1995 and 2005 were identified from the Vera Moulton Wall Center Pulmonary Arterial Hypertension database.
- At the time of query, our database (n=384) included detailed information for initial and each clinic visit, demographics, WHO PAH classification, concomitant illnesses, medical and surgical history, family history, medications, exposure to stimulants or anorexigens, NYHA class, exercise capacity (6MWT), body-mass index (BMI) and diagnostic test results (including pulmonary function tests, echocardiograms, right heart catheterizations, ventilation/perfusion (V/Q) scans, polysomnograms and chest computed tomography).
- A case-control matched analysis was made comparing PAH patients exposed to anorexigens and/or stimulants (n=20) and PAH patients without an exposure (n=20).
- Patients were matched based on age, gender, ethnicity, concomitant medications, Borg dyspnea index, and hemodynamic variables.
- Patient charts were reviewed to verify data about demographics, 6MWT, NYHA classification, and start date of bosentan.
- All PAH patients in the database who had an exposure to anorexigens and/or stimulants and were treated with the endothelin receptor antagonist bosentan for at least 3 months were included in the study.
- Patients were excluded if bosentan therapy was interrupted in the evaluation period. Patients were excluded from the final analysis if they did not have a 6MWT and NYHA class status after 3 months of bosentan treatment
- The primary outcome was the change in 6 minute walk test before and after treatment.
- Secondary outcomes included change in NYHA classification, and clinical outcomes including death, lung transplantation and addition of other therapies.
- Statistical analysis was performed using unpaired Student's t-test with Welch's correlation, assuming equal variance. An ANOVA test was performed to test the validity of the equal-variances assumption. A p value of < 0.05 was deemed statistically significant.

Results

Table 1 *Baseline Patient Characteristics*

Demographic variables	Anorexigen and/or Stimulant Exposure (n=20)	No Anorexigen and/or Stimulant Exposure (n=20)	p
Age – yrs	47.3 ± 1.9	43.7 ± 3.5	0.38
Weight – Kg	84 ± 3.8	79 ± 4.9	0.41
Sex- No. (%):			
Male	2 (10)	3 (15)	-
Female	18 (90)	17 (85)	-
Ethnic group - no. (%):			
White	19 (95)	15 (75)	-
Other	1 (5)	5 (25)	-
Etiology of PAH - no. (%):			
Idiopathic PAH	8 (40)	8 (40)	-
Congenital heart disease	1 (5)	3 (15)	-
Collagen vascular disease	2 (10)	2 (10)	-
Hypoxemic lung disease	5 (25)	5 (25)	-
Chronic thromboembolic disease	3 (15)	2 (10)	-
HIV	1 (5)	0	-
WHO functional class - No. (%):			
III	13 (65)	13 (65)	-
IV	7 (35)	7 (35)	-
6-Min Walk Distance – Meters	343 ± 34	434 ± 19	0.03
Borg Dyspnea index	1.1 ± 0.3	1.4 ± 0.2	0.86
Concomitant treatment - No. (%):			
Warfarin	19 (95)	18 (90)	-
Diuretics	20 (100)	16 (80)	-
Calcium channel blockers	11 (55)	6 (30)	-
Supplemental oxygen	11 (55)	15 (75)	-
Epoprostenol	9 (45)	8 (45)	-
Treprostenol	4 (20)	1 (5)	-
Sildenafil	5 (25)	0	-
Time since diagnosis - Months	48 ± 2.7	42 ± 3.6	0.2
Hemodynamic variables:			
Mean RA pressure (mmHg)	11.5 ± 1	9.8 ± 0.9	0.41
Mean PAP (mmHg)	57 ± 0.9	56 ± 3	0.85
Mean PCWP (mmHg)	11 ± 0.4	8.8 ± 0.5	0.03
Cardiac index (L/min/m^2)	1.8 ± 0.07	2 ± 0.05	0.11
PVR (dynes/cm^5)	987 ± 37	877 ± 92	0.47

Table 1: ***Baseline Characteristics of PAH Patients:*** Both patient groups were well matched with respect to demographics, hemodynamics and other baseline characteristics. Patients were classified as IPAH if they had no other clear PAH risk factor or associated disease; 40% of the anorexigen and/or stimulant exposed patients had no other risk factor or condition associated with PAH, the same as the unexposed group. Most patients in both groups were NYHA class III at baseline. Both groups had similar concomitant medications and time since diagnosis. Hypoxemic lung diseases included COPD and OSA. All numeric variables are represented as Mean ± SEM. *PAH = Pulmonary Arterial Hypertension, HIV = Human Immunodeficiency Virus, WHO = World Health Organization, RA = Right Atrium; PAP = Pulmonary Artery Pressure, PCWP = Pulmonary Capillary Wedge Pressure; PVR = Pulmonary Vascular Resistance.*

Fig 1 *6 Min Walk Test*

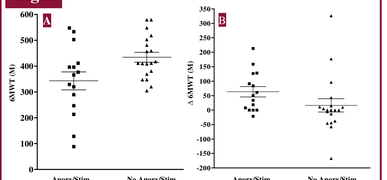

Fig 1: ***Exercise capacity characterized by the 6-Minute Walk Test:*** (A) Exposed PAH patients had worse baseline 6MWT compared to non-exposed patients by a mean distance 91 ± 30 M (p = 0.03). (B) After 12 weeks of treatment with bosentan, anorexigen and/or stimulant exposed PAH patients experienced a mean change of 63 ± 17 M whereas non-exposed patients experienced only a mean change of 16 ± 23 M (p = 0.11). Data presented in Mean ± SEM.
Anorx/stim: Anorexigen and/or stimulant

Fig 2 *NYHA Change*

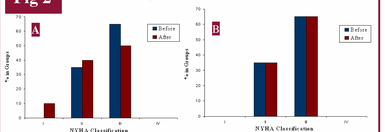

Fig 2: ***Change in Functional capacity based on NYHA change****: (A) NYHA Classification Profile of anorexigen exposed PAH patients before and after 12-week treatment with bosentan:* 10% improved to WHO class I. *(B) PAH patients not exposed to anorexigens before and after 12-week treatment with bosentan:* No improvement in WHO class

Fig 3 *Ceiling Effect*

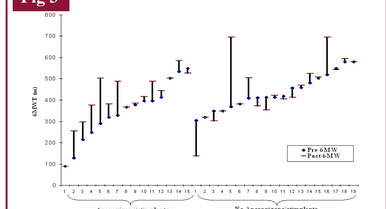

Fig 3: ***Individual change in 6MWT***: Non-exposed PAH patients showing blunted response to bosentan

Discussion

- Though the precise mechanism by which anorexigens and/or stimulants lead to PAH is poorly understood, several theories have been suggested including alteration in serotonin metabolism, direct pulmonary vasoconstriction, and genetic susceptibility [6].
- While patients who were exposed to anorexigens and/or stimulants had poorer baseline 6MWT and appeared to have a better response to 12 weeks of treatment with bosentan, the data on 6 MWT did not achieve statistical significance. It may be that the response to endothelin receptor antagonism appears brisker in exposed patients because of a background of more rapid disease progression and deterioration.
- Despite the lack of statistical significance with respect to 6MWT there was a significant improvement in NYHA class in the exposed versus the unexposed patients following treatment with an ERA.
- The anorexigen and/or stimulant exposed PAH patients suffered worse clinical outcomes. Two patients in the anorexigen/stimulant exposed group died while there were no deaths in the nonexposed group during the study period.

Conclusion

- Our analysis hints at a better response in 6-minute walk distance and NYHA classification after 3 months of treatment with bosentan in patients history of exposure to anorexigens and/or stimulants but perhaps worse clinical outcomes overall.
- This study suggests the need for a better understanding of the pathogenesis of PAH, including PAH related to anorexigen and/or stimulant use, and the need to more closely assess the efficacy of ERAs in this subset of PAH patients.

References

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