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Selective serotonin reuptake inhibitor use and outcomes in pulmonary arterial hypertension ☆

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Abstract

Background: Pulmonary arterial hypertension (PAH) is characterized by elevated pulmonary vascular resistance which leads to right ventricular failure. Serotonin and the serotonin transporter play an important role in animal and human studies of PAH. We therefore hypothesized that PAH patients treated with high-affinity selective serotonin reuptake inhibitors (SSRIs) would have a reduced risk of death compared to PAH patients not treated with SSRIs.

Methods: We performed a retrospective cohort study of 84 consecutive adult PAH patients who underwent initial evaluation from January 1994 to June 2002 at the Pulmonary Hypertension Center of the New York Presbyterian Hospital. Patient–time while receiving high-affinity SSRIs ($K_d < 1$ nmol) (paroxetine, sertraline, or fluoxetine) was considered ''exposed''. Patient–time while receiving tricyclic, atypical, or no antidepressants was considered ''unexposed''.

Results: Thirteen of the 84 patients (15%) used high-affinity SSRIs during the study period. Five patients were taking high-affinity SSRIs at baseline and 8 initiated high-affinity SSRIs during the follow-up period. The median time from baseline evaluation until initiation of high-affinity SSRIs was 125 (0–1227) days. The median duration of high-affinity SSRI use was 482 (110–1624) days and the total at-risk time on high-affinity SSRIs was 18.1 person-years. Seventy-nine (94%) patients were treated with warfarin; 38 (45%) received continuous intravenous epoprostenol; 12 (14%) received continuous subcutaneous treprostinil, and 23 (27%) were treated with oral bosentan. The median follow-up was 764 days. Twenty-four patients died and one underwent lung transplantation during the study period.

There were no differences in age, gender, diagnosis, hemodynamics, or incidence of acute vasoreactivity between SSRI users and non-users. The risk of death for high-affinity SSRI users was lower but not statistically significantly different from that of non-users (hazard ratio = 0.53, 95% CI 0.07 to 3.9, $p = 0.53$). Adjustment for demographics, diagnosis, hemodynamics, or other therapies did not significantly change this result.

Conclusions: SSRI use was associated with a 50% reduction in the risk of death in a cohort of PAH patients which was not statistically significant. Larger cohort studies may better define this relationship; an adequately powered trial of high-affinity SSRIs in PAH patients may be warranted.

Keywords: Hypertension; Pulmonary; Serotonin; Therapy; Serotonin uptake inhibitors

Abbreviation: CI, confidence interval; HR, hazard ratio; PAH, pulmonary arterial hypertension; SERT, serotonin transporter; SSRI, selective serotonin reuptake inhibitor

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1. Introduction

Pulmonary arterial hypertension (PAH) is characterized by elevated pulmonary vascular resistance and right ventricular failure. Many studies support a role for serotonin in the pathophysiology of PAH. Patients with PAH have increased free plasma serotonin levels, which persist beyond explantation of the diseased lungs [1]. Overexpression of the gene for the serotonin transporter (SERT), which brings serotonin into cells, results in increased pulmonary artery pressure [2]. Hypoxia- and monocrotaline-induced pulmonary hypertension in animal models is inhibited by fluoxetine, a selective serotonin reuptake inhibitor (SSRI) that blocks the SERT [3,4]. Studies have also suggested a protective effect of SSRI use in coronary artery disease [5–7]. Although these findings provide a rationale for randomized controlled trials of SSRIs in PAH, there are no published clinical data regarding SSRI use in PAH patients, making a clinical trial premature. We hypothesized that PAH patients treated with high-affinity SSRIs would have a reduced risk of death compared to PAH patients not treated with SSRIs.

2. Materials and methods

2.1. Study subjects

The subjects were patients who underwent initial evaluation between January 1994 and June 2002 at the Pulmonary Hypertension Center of the New York Presbyterian Hospital. We included adult (>16-year old) patients with PAH which was idiopathic, familial, or associated with anorexigen use. Patients who were diagnosed with PAH related to connective tissue diseases, portal hypertension, HIV infection, or congenital heart disease were excluded. We also excluded patients who underwent initial evaluation and treatment at other centers to prevent bias introduced by selective referral. The study was approved by the Columbia University Medical Center Institutional Review Board.

2.2. Study design

We performed a retrospective cohort study of consecutive adult PAH patients who met our inclusion criteria. Patient–time while receiving high-affinity SSRIs ($K_d < 1$ nmol) (paroxetine, sertraline, or fluoxetine) was considered "exposed" [7]. Patient–time while receiving tricyclic, atypical, or no antidepressants was considered "unexposed". Patients were censored at the time of initiation of moderate-affinity SSRIs (K_d 1–10 nmol) (citalopram and fluvoxamine). Acute pulmonary vasoreactivity was defined as a drop in mean pulmonary artery pressure of at least 10 mm Hg to $\leqslant$40 mm Hg with no change or an increase in cardiac index after vasodilator administration [8]. The primary endpoint was time until death or lung transplantation through June 30, 2003.

2.3. Statistical analysis

Continuous variables were summarized by the mean (standard deviation) or median (range). Categorical variables were summarized by frequencies with 95% confidence intervals (95% CIs). *T*-tests, Wilcoxon rank-sum tests, and Fisher's exact tests were used, as appropriate. Bivariate and multivariate survival analyses were performed using Cox proportional hazards models [9]. SSRI use was modeled as a time-varying covariate, which allowed us to consider patient–time while not receiving SSRIs as "unexposed" and patient–time while receiving SSRIs as "exposed". Simple imputation was performed for covariates with missing data in the multivariate analyses. Patients without acute vasodilator testing were presumed to not have acute pulmonary vasoreactivity in the multivariate analysis. *p*-Values <0.05 were considered statistically significant. Stata version 7.0 (Stata Corp., College Station, TX) was used for all analyses.

3. Results

The cohort included 84 patients. The mean age was 42 (14) years. Sixty-one (81%) patients were female. Eighty patients underwent right heart catheterization, and 74 had acute pulmonary vasodilator testing performed during right heart catheterization. Seventy-nine (94%) patients were treated with warfarin; 72 (86%) received digoxin; 38 (45%) received continuous intravenous epoprostenol; 12 (14%) received continuous subcutaneous treprostinil; and 23 (27%) were treated with oral bosentan. The median follow-up was 764 [interquartile range, 505, 1573] days. Twenty-four patients died and one underwent lung transplantation during the study period. One-year survival was 87% (95% CI 77–93%) and 5-year survival was 61% (95% CI 45–73%).

Thirteen patients (15%, 95% CI 9–25%) were treated with high-affinity SSRIs (Table 1) and 2 patients (2%) were treated with moderate-affinity SSRIs during the study period. Five patients were taking high-affinity SSRIs at baseline and 8 initiated high-affinity SSRIs during the follow-up period. The median time from baseline evaluation until initiation of high-affinity SSRIs was 125 (0–1227) days; half of the patients in the cohort treated with SSRIs initiated therapy several months after starting PAH treatment. The median duration of high-affinity SSRI use was 482 (110–1624) days, and the total at-risk time on high-affinity SSRIs was 18.1 person-years.

Demographics and baseline hemodynamics for patients treated with high-affinity SSRIs were compared to those of the SSRI non-users (Table 2). All of the patients treated with high-affinity SSRIs had idiopathic PAH. There were no significant differences in age, gender, hemodynamic