RESEARCH LETTER

Pentoxifylline Therapy for Hepatopulmonary Syndrome: A Pilot Study

Hepatopulmonary syndrome (HPS) is characterized by a triad of liver disease, hypoxemia, and intrapulmonary vascular dilations (IPVDs). Its prevalence is 4% to 47% in patients with cirrhosis. Patients with HPS demonstrate a significant reduction in exercise capacity due to abnormal pulmonary circulation. Anatomic arteriovenous shunts in the lung are used during exercise and lead to exercise-induced impairment in gas exchange and exercise-induced arterial hypoxemia.

The pathogenesis of HPS is unclear. Cytokine-mediated injury is alleged to play a key role. Endothelin-1 and tumor necrosis factor (TNF) interaction, occurring in the lung vasculature, contribute to the development of experimental HPS. Overproduction of TNF, due to endotoxin stimulation of Kupffer cells, might be a major mechanism leading to HPS.

Pentoxifylline, a nonspecific phosphodiesterase-4 inhibitor, blocks TNF synthesis and TNF-induced macrophagic nitric oxide production. Pentoxifylline prevented the development of HPS and attenuated HPS in cirrhotic rats. However, to our knowledge, pentoxifylline has not been used clinically for the treatment of HPS. In this study, we tried pentoxifylline therapy in patients with HPS.

Methods. Patients. This was an open-label, prospective, nonrandomized clinical trial to study the efficacy and safety of pentoxifylline therapy for HPS. A consecutive series of patients with cirrhosis attending our hospital were screened. Hepatopulmonary syndrome was diagnosed according to the European Respiratory Society Task Force criteria of PaO2 less than 80 mm Hg plus positive contrast-enhanced echocardiography (CEE). Subclinical HPS was diagnosed when CEE was positive but PaO2 was 80 to 90 mm Hg (to convert to kilopascals, multiply by 0.133). Patients with intrinsic cardiopulmonary disease, hepatic encephalopathy, and malignant neoplasms were excluded. The study was approved by an institutional ethics committee, and informed consent was obtained from each patient before enrollment.

Pentoxifylline Treatment. Pentoxifylline was given in a dosage of 400 mg, 3 times daily for 3 months. Patients were monitored for any adverse effects.

Investigations. Cirrhosis was diagnosed by clinical, biochemical, histological, or imaging studies. Viral serologic and other tests were performed to find the cause. Upper gastrointestinal endoscopy and hepatic venous pressure gradient measurements were performed to assess portal hypertension. Chest radiography and pulmonary function tests were performed to exclude chest diseases.

Contrast-enhanced echocardiography was performed with 10 mL of agitated isotonic sodium chloride solution injected in the antecubital vein. The appearance of air bubbles in the left side of the heart after the third beat following the initial appearance in the right side of the heart was considered a positive test result (CEE+).

PaO2 was measured with the patient in the supine position, breathing room temperature air, after resting for 15 minutes. PaO2 was also measured immediately after standing from supine position, and after lowest level 10-minute exercise on treadmill according to Bruce protocol. Exercise-induced change in blood oxygen (EICBO) was calculated as follows:

\[
EICBO = \left( \frac{\text{PaO}_2 \text{ Exercise} - \text{PaO}_2 \text{ Standing}}{\text{PaO}_2 \text{ Standing}} \right) \times 100.
\]

The frequency of patients having exercise-induced arterial hypoxemia was also determined.

Pretherpay and posttherapy serum TNF levels were determined using commercially available enzyme-linked immunosorbent assay kits (Anogen, Mississauga, Ontario, Canada).

Response to Therapy. Response to pentoxifylline therapy, assessed at 3 months, was defined as the following:

- Complete response: An increase in PaO2 by greater than 10 mm Hg from baseline level or a PaO2 of 80 mm Hg or greater.
- Partial response: An increase in PaO2 by 5 to 10 mm Hg from baseline, but a PaO2 lower than 80 mm Hg.
- No response: An increase in PaO2 by less than 5 mm Hg, no increase, or a decrease in PaO2 from baseline.
- Primary end point: Achievement of complete response at 3 months of therapy.
- Secondary end points: Development of serious adverse effects leading to withdrawal of the drug or death from any cause.

Statistical Analysis. For comparison of parameters pretherapy and posttherapy, the Wilcoxon signed rank test was used. \( P < .05 \) was considered significant. SPSS version 15.0 statistical software (SPSS Inc, Chicago, Illinois) was used for analysis.

Results. Patients. A total of 251 patients with cirrhosis were screened for the presence of HPS from April 2005 through September 2006. Seventeen patients were excluded because 9 had hepatic encephalopathy, 4 had he-
Patocellular carcinoma, 3 had pleural effusion, and 1 had rheumatic heart disease. Of the remaining 234 patients, 71 (30%) were CEE*. Of these, 21 patients had HPS and 50 had subclinical HPS. Of 21 patients with HPS, 9 could be included in the trial. Twelve patients could not participate because 5 died before inclusion, 4 refused to participate, and 3 were lost to follow-up before inclusion. The baseline clinical and laboratory characteristics of included patients are given in Table 1.

Response to Pentoxifylline. Clinical. Pretherapy clubbing was seen in all 9 patients (100%), dyspnea and cyanosis were found in 8 patients (89%), palmar erythema was found in 5 patients (56%), and platypnea was found in 3 patients (33%). All 9 patients completed 3 months of therapy. Clinically, there was moderate to marked improvement in dyspnea, cyanosis, and palmar erythema in 8 of 9 patients (89%). Platypnea improved in all 3 patients. One patient (11%) did not show any improvement in any symptoms and signs.

PaO2 Levels. There were 8 complete responders (89%) and 1 nonresponder (11%) to therapy. The median baseline PaO2 levels (ranges) were 73 (54-74) mm Hg with patients in the supine position, 68 (48-72) mm Hg while standing, and 60 (35-65) mm Hg after exercise (Table 2). This dip in PaO2 level with standing and exercise was seen in all the patients. With treatment, there was a significant (P < .01) increase in median (range) supine, standing, and postexercise PaO2 values (82 [56-89] mm Hg; 83 [51-94] mm Hg, and 74 [37-100] mm Hg, respectively) (Table 2 and Figure 1).

At baseline, 7 of 9 patients (78%) had orthodeoxia, and after therapy, orthodeoxia resolved in 3 of these 7 patients (43%).

The individual EICBO values in patients are shown in Figure 2. The median (range) pretherapy EICBO was −13.9% (−29.7% to −7.1%), which increased to −7.5% (−27.4 to 5.9%) after therapy (P = .01). Before therapy, all patients had exercise-induced arterial hypoxemia. However, after therapy, only 6 had exercise-induced arterial hypoxemia (P = .21).

TNF Levels. After completing 3 months of therapy, the median (range) TNF levels decreased significantly (19.8 [5.5-39.6] pg/mL vs 14.5 [5.1-27.9] pg/mL) (P = .02) (Table 2 and Figure 3).

Table 1. Baseline Parameters of Patients With HPS Included in the Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>40 (18-52)</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>5/4</td>
</tr>
<tr>
<td>Dyspnea, No. (%)</td>
<td>8 (89)</td>
</tr>
<tr>
<td>Platypnea, No. (%)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Cyanosis, No. (%)</td>
<td>8 (89)</td>
</tr>
<tr>
<td>Clubbing, No. (%)</td>
<td>9 (100)</td>
</tr>
<tr>
<td>Spider angiomas, No. (%)</td>
<td>7 (78)</td>
</tr>
<tr>
<td>Palmar erythema, No. (%)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>Hemoglobin, mean (SD), g/dL</td>
<td>10.8 (2.1)</td>
</tr>
<tr>
<td>Serum creatinine, mean (SD), mg/dL</td>
<td>0.8 (0.4)</td>
</tr>
<tr>
<td>Serum bilirubin, mean (SD), mg/dL</td>
<td>2.0 (1.3)</td>
</tr>
<tr>
<td>Serum albumin, mean (SD), g/dL</td>
<td>3.1 (0.5)</td>
</tr>
<tr>
<td>INR, mean (SD)</td>
<td>1.8 (0.4)</td>
</tr>
<tr>
<td>Cause of cirrhosis, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Budd-Chiari syndrome</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Child-Pugh score, mean (SD)</td>
<td>9.0 (1.1)</td>
</tr>
<tr>
<td>MELD score, mean (SD)</td>
<td>15.3 (3.2)</td>
</tr>
<tr>
<td>HVPG, mean (SD), mm Hg</td>
<td>17.3 (6.4)</td>
</tr>
</tbody>
</table>

Abbreviations: HVPG, hepatic venous pressure gradient; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease.

Table 2. Comparison of Pretreatment and Posttreatment PaO2, TNF, EICBO, and EIAH

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine PaO2, median (range), mm Hg</td>
<td>73 (54 to 74)</td>
<td>82 (56 to 89)</td>
<td>.008</td>
</tr>
<tr>
<td>Standing PaO2, median (range), mm Hg</td>
<td>68 (48 to 72)</td>
<td>83 (51 to 94)</td>
<td>.008</td>
</tr>
<tr>
<td>Postexercise PaO2, median (range), mm Hg</td>
<td>60 (35 to 65)</td>
<td>74 (37 to 100)</td>
<td>.008</td>
</tr>
<tr>
<td>Serum TNF level, median (range), pg/mL</td>
<td>19.8 (5.5 to 39.6)</td>
<td>14.5 (5.1 to 27.9)</td>
<td>.02</td>
</tr>
<tr>
<td>EICBO, median (range), %</td>
<td>−13.9 (−29.7 to −7.1)</td>
<td>−7.5 (−27.4 to 5.9)</td>
<td>.01</td>
</tr>
<tr>
<td>Patients with EIAH, No./Total No. (%)</td>
<td>9/9 (100)</td>
<td>6/9 (67)</td>
<td>.21</td>
</tr>
</tbody>
</table>

Abbreviations: EICBO, exercise-induced change in blood oxygen; EIAH, exercise-induced arterial hypoxemia; TNF, tumor necrosis factor. SI conversion factor: To convert PaO2 to kilopascals, multiply by 0.133.
ADVERSE EFFECTS. Three patients developed transient vomiting, and 2 reported dyspeptic symptoms after pentoxifylline treatment. These subsided with symptomatic treatment. There were no severe adverse effects. There were no significant changes in liver function tests due to treatment with pentoxifylline.

Comment. Our results demonstrate that in patients with HPS, 3 months of treatment with pentoxifylline achieves a significant therapeutic response, with improvement in symptoms and signs in approximately 90% of patients. Furthermore, the exercise tolerance of patients improved, as indicated by an increase in EICBO and reversal of exercise-induced arterial hypoxemia.

The clinical features of HPS typically involve respiratory complaints including cyanosis, dyspnea, platypnea, orthodeoxia (fall in PaO₂ ≥5% or ≥4 mm Hg while standing), and clubbing. Diagnosis of HPS is based on arterial deoxygenation and CEE in the absence of intrinsic cardiopulmonary disease. We used this criterion to diagnose HPS.

Liver transplantation is the only established effective therapy for HPS. However, mortality is increased after transplantation in patients who have HPS, and transplantation is not uniformly effective in reversing HPS. To our knowledge, there is currently no effective medical therapy for HPS. Small uncontrolled studies have reported a lack of efficacy with the use of sympathomimetics, somatostatin, almitrine, indomethacin, and plasma exchange. Reports using garlic, aspirin, and nitric oxide inhibitor showed variable results. These reports underscore the need to evaluate agents targeting pathogenetic mechanisms of HPS to determine efficacy.

The overproduction of nitric oxide in lungs of patients with cirrhosis is ascribable to intravascular macrophage induction of inducible nitric oxide synthase, which accumulates in the pulmonary vasculature. Since TNF is a potent inducible nitric oxide synthase activator in macrophages, TNF inhibition might prevent pulmonary nitric oxide overproduction, thereby preventing or attenuating HPS. Pentoxifylline blocks TNF synthesis and TNF-induced macrophagic production. Sztrymf et al have shown that inhibition of TNF with pentoxifylline in cirrhotic rats prevents development of hyperdynamic circulatory state and HPS. Moreover, pentoxifylline attenuated experimental HPS. The results of the present study show a very encouraging response to pentoxifylline therapy in patients with HPS, and the improvement in symptoms and PaO₂ provides proof of principle.

Pentoxifylline also improved exercise tolerance. Before therapy, all patients had a decrease in their blood oxygen content during exercise, with a median EICBO of −13.9%. With treatment, the median EICBO significantly increased to −7.5%. Moreover, exercise-induced arterial hypoxemia reversed in 3 patients.

In animal studies, the dosage of pentoxifylline used was 10 to 50 mg/kg/d. We used 400 mg, 3 times daily (approximately 20 mg/kg/d), which is the dosage currently approved by the Food and Drug Administration. A proper dose-finding study would be needed to determine the optimum dose for use in HPS. The adverse effects of pentoxifylline were few, nonserious, and easily manageable and did not require drug withdrawal.

There were a few limitations in our study. First, we did not have a control group of patients for TNF levels, ie, cirrhotic patients without HPS. Our assumption that TNF levels are high in cirrhotic patients with HPS compared with cirrhotic patients without HPS was based on previous animal studies. Moreover, with pentoxifylline therapy, improvement in HPS symptoms correlated with a decrease in TNF levels. Second, we had only 9 patients in our study. Classic HPS is rare, while subclinical HPS is more common. In a period of 18 months, only 21 pa-
ponents fit the criteria for HPS, while we found 50 patients with subclinical HPS. Third, this was an open-label trial without any comparator group receiving placebo. Although recommendations cannot be formed based on this open-label pilot study of just 9 patients, larger randomized controlled trials can be initiated based on the encouraging results of the present study.

In conclusion, our results suggest that pentoxifylline can be considered a safe and effective therapy for HPS. Further trials should address the issues of using higher dosage, longer duration, and combination with other drugs and whether its use can prevent progression of subclinical HPS.

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Financial Disclosure: None reported.


COMMENTS AND OPINIONS

Mediterranean Diet and Mortality in a US Population

In a recent study of a US population, Mitrou et al reported longer survival for subjects conforming more to the Mediterranean Diet (MeDi). A few months earlier, we had demonstrated that higher adherence to the MeDi was associated with reduced mortality in community-based Alzheimer disease (AD) patients who were identified in another US population in New York, New York. Considering subjects from the same New York study, we had previously demonstrated that higher conformity to the MeDi was also associated with reduced risk for AD. In a different New York population, we have also showed that higher MeDi adherence is related to a lower odds for essential tremor.

Prompted by the study by Mitrou et al, we investigated the association between MeDi adherence (calculated using the same method) and all-cause mortality in our community-based multiethnic population study of subjects 65 years or older in New York. Baseline dietary evaluations and follow-up data were available for 2769 subjects, 764 of whom died during the mean (SD) course of 5 (3.3) years of follow-up. Compared with subjects in the lower tertile of MeDi adherence, mortality hazard ratios (HRs) were 0.83 (95% confidence interval [CI], 0.71-0.97) for those in the middle tertile and 0.61 (95% CI, 0.50-0.75) for those in the highest tertile (P for trend, <.001). Median survival times were 9.2 years for the lower tertile, 10.2 years for the middle tertile, and 12.1 years for the highest tertile of MeDi adherence. In stratified analyses, the association was stronger for Hispanics but was present for all ethnicities: whites (n=723), middle tertile HR, 0.82 (95% CI, 0.59-1.13), and high tertile HR, 0.57 (95% CI, 0.37-0.89) (P for trend, 0.01); blacks (n=905), middle tertile HR, 0.89 (95% CI, 0.67-1.14), and high ter-