

## Pentoxifylline in hepatopulmonary syndrome

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**RESULTS:** Six patients could tolerate PTX, while four patients experienced complications. Among patients who could tolerate PTX, there was a significant increase in arterial oxygen pressure (PaO<sub>2</sub>) ( $P = 0.02$ ) and oxygen saturation (SaO<sub>2</sub>) ( $P = 0.04$ ) and alveolar-arterial oxygen gradient ( $P = 0.02$ ) after 3 mo of treatment. Significant decreases in PaO<sub>2</sub> ( $P = 0.02$ ) and alveolar-arterial oxygen gradient ( $P = 0.02$ ) were also seen after drug discontinuation.

**CONCLUSION:** PTX may improve PaO<sub>2</sub>, SaO<sub>2</sub> and alveolar-arterial oxygen gradient in the early stage of HPS.

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**Key words:** Pentoxifylline; Hepatopulmonary syndrome; Child; Arterial oxygen pressure; Therapy; Alveolar-arterial oxygen gradient

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### Abstract

**AIM:** To determine the effects of pentoxifylline (PTX) on clinical manifestations and evaluate arterial blood gas data in hepatopulmonary syndrome (HPS) in children.

**METHODS:** In a pilot study of 10 children with chronic liver disease, who had HPS, 20 mg/kg/d PTX was administered for 3 mo. Clinical data and arterial blood gas parameters were evaluated at baseline, the end of the treatment period, and 3 mo after drug discontinuation.

### INTRODUCTION

The hepatopulmonary syndrome (HPS) is the triad of liver disease, arterial hypoxemia and widespread pulmonary vascular dilatation<sup>[1-3]</sup>. Prevalence of this syndrome is 10%-30% among patients with chronic liver disease<sup>[4]</sup>.

The pathogenesis of HPS is unclear. The roles of eicosanoids as vasoconstrictors and the increased number of intravascular macrophage-like cells have been reported previously. Increased pulmonary production of NO in

cirrhosis has been considered as a reason for intrapulmonary venous dilatation. It is claimed that increased pulmonary NO production is due to raised pulmonary vascular endothelial NO synthase (eNOS) and inducible NO synthase expression. Recent studies have shown that increased hepatic production and release of low level of endothelin 1 (ET-1) can act as a trigger for enhancing eNO level. Tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) and ET-1 have been implicated in the development of experimental HPS. Recent studies have suggested that progression of HPS is due to increased CO production and heme oxygenase 1 expression<sup>[5-7]</sup>. The presence of HPS increases mortality in cirrhotic patients and may influence the frequency and severity of complications of portal hypertension<sup>[8-11]</sup>. To the best of our knowledge, there is currently no effective medical therapy for HPS. Several medications such as methylene blue, garlic and aspirin have been reported to have a therapeutic effect<sup>[12-15]</sup>, but curative treatment of this syndrome is still orthotopic liver transplantation<sup>[16]</sup>.

Pentoxifylline (PTX), a nonspecific phosphodiesterase-4 inhibitor, blocks TNF $\alpha$  synthesis<sup>[17,18]</sup> and seems to prevent HPS. There are limited studies about PTX in adult patients with HPS, with varying results. Until now, no study has been carried out in children. The aim of this study was to evaluate the effect of PTX on clinical manifestations and arterial blood gas data in children with HPS.

## MATERIALS AND METHODS

This pilot study was carried out in the Ghaem Medical Center of Mashhad University of Medical Sciences, Iran during a 21-mo period (March 2008-November 2010). The protocol for this study was approved by the Ethics Committee of Mashhad University. Children and their parents were given informed consent forms. A consecutive series of patients with cirrhosis attending our hospital were screened for HPS. HPS was diagnosed according to the European Respiratory Society Task Force criteria: hypoxemia plus positive contrast-enhanced echocardiography<sup>[7]</sup>. Positive contrast echocardiography was defined by the appearance of air bubbles in the left side of the heart after the first three beats during injection of 10 mL agitated isotonic saline solution in the antecubital vein<sup>[19]</sup>. Exclusion criteria were active infection, known malignancy, cardiac disease, and kidney disease.

Patient data including demographics, etiology of cirrhosis, clinical manifestations, laboratory results [complete blood count (CBC), diff, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, prothrombin time, partial thromboplastin time, total bilirubin, direct bilirubin, albumin and total protein] were recorded. For each patient, Child score was determined. All patients underwent measurement of arterial oxygen pressure (PaO<sub>2</sub>) and oxygen saturation (SaO<sub>2</sub>) by blood sampling from the radial artery in a sitting position while breathing ambient air. For each

Table 1 Baseline patient characteristics *n* (%)

Variable	Value ( <i>n</i> = 10)
Age (yr)	
Mean $\pm$ SD, (range)	9.2 $\pm$ 5.0 (2-16)
Sex	
Female/male	4/6
Cause of cirrhosis	
Wilson disease	3 (30)
Cryptogenic cirrhosis	3 (30)
Autoimmune hepatitis	2 (20)
PFIC	1 (10)
GSD	1 (10)
Staging of HPS	
Mild	2 (20)
Moderate	6 (60)
Severe	1 (10)
Very severe	1 (10)
Child score	
A	3 (30)
B	4 (40)
C	3 (30)

PFIC: Progressive familial intrahepatic cholestasis; GSD: Glycogen storage disease; HPS: Hepatopulmonary syndrome.

patient, alveolar-arterial oxygen gradient was calculated. Patients were classified in four groups according to severity of hypoxemia: mild HPS with PaO<sub>2</sub>  $\geq$  80 mmHg, moderate HPS with 60  $\leq$  PaO<sub>2</sub> < 80 mmHg, severe HPS with 50  $\leq$  PaO<sub>2</sub> < 60 mmHg, and very severe HPS with PaO<sub>2</sub> < 50 mmHg<sup>[7]</sup>.

PTX at a dose of 20 mg/kg per day orally in three divided doses was administered for 3 mo. In this period, patients were followed up weekly and whenever patients required, by telephone conference and monthly with outpatient visits. Clinical manifestations and laboratory data were rechecked at the end of the treatment period, 3 mo after drug discontinuation and whenever a child had any deterioration or could not tolerate PTX. Response to PTX was considered as increased PaO<sub>2</sub> > 10 mmHg from baseline<sup>[20]</sup>. Complement a three months period of treatment was considered as primary end point and development of serious side effects, death and liver transplantation was considered as the secondary end point.

After entering data into SPSS version 16.0 software, quantitative data were analyzed by the Wilcoxon signed rank test and qualitative data by the McNemar test. A *P* value < 0.05 was considered significant.

## RESULTS

A total of 65 patients aged < 18 years with cirrhosis were screened for the presence of HPS from March to August 2009. Twelve patients had HPS. Two were excluded. One had kidney disease and one did not allow us to intervene. Ten children were enrolled. Two patients had mild HPS, six moderate HPS, one severe HPS and one very severe HPS. Four patients were girls. Mean age was 9.2  $\pm$  5.0 years old. The most common recognized cause of cirrhosis was Wilson's disease (Table 1). Minimum alveolar-

**Table 2** Clinical and laboratory data at baseline and end of treatment period (mean  $\pm$  SD) *n* (%)

Variable	Baseline	End of treatment	<i>P</i> value
Clinical manifestations			
Cyanosis	9 (90)	5 (50)	0.12
Dyspnea	3 (30)	2 (20)	1.0
Clubbing	7 (70)	7 (70)	1.0
Palmar erythema	5 (50)	5 (50)	1.0
Hepatomegaly	6 (60)	6 (60)	1.0
Splenomegaly	7 (70)	7 (70)	1.0
Laboratory findings			
White blood cell count, $\times 10^3/\text{mm}^3$	6.4 $\pm$ 4.41	4.36 $\pm$ 2.04	0.17
Hemoglobin, g/dL	11.25 $\pm$ 2.30	11.45 $\pm$ 2.71	0.49
Platelet count, $\times 10^3/\text{mm}^3$	131.6 $\pm$ 566.74	156.2 $\pm$ 498.36	0.32
Serum creatinine, mg/dL	0.56 $\pm$ 0.16	0.6 $\pm$ 0.14	1.0
Serum urea, g/dL	12.60 $\pm$ 5.98	14.70 $\pm$ 7.20	0.34
Serum albumin, g/dL	3.88 $\pm$ 0.52	3.56 $\pm$ 0.15	0.59
Serum total protein, g/dL	7.20 $\pm$ 0.40	7.26 $\pm$ 0.81	1.0
PT, s	15.72 $\pm$ 3.07	18.51 $\pm$ 8.27	0.40
PTT, s	45.50 $\pm$ 14.54	49.42 $\pm$ 11.41	0.24
INR	1.46 $\pm$ 0.36	1.90 $\pm$ 1.14	0.67
Total bilirubin, mg/dL	5.73 $\pm$ 7.39	5.07 $\pm$ 6.04	0.17
Direct bilirubin, mg/dL	1.70 $\pm$ 2.50	1.68 $\pm$ 2.71	0.83
ALT, U/L	83.60 $\pm$ 64.28	40.60 $\pm$ 31.56	0.27
AST, U/L	92.55 $\pm$ 64.48	66.80 $\pm$ 2814	0.50
ALP, U/L	564.66 $\pm$ 198.74	536.50 $\pm$ 17.67	0.18

PT: Prothrombin time; PTT: Partial thromboplastin time; INR: International normalized ratio; ALT: Alaninaminotransferase; AST: Aspartataminotransferase; ALP: Alkaline phosphatase.

arterial oxygen gradient at baseline was 18.84 and maximum was 71.98. Clinical and laboratory characteristics of the patients at baseline and end of treatment period are summarized in Table 2.

Six patients completed the treatment period. Petechiae with platelet count  $10\,000/\text{mm}^3$  was seen in one patient, 3 wk after the beginning of PTX. He was a 16-year-old boy with Wilson's disease and very severe HPS. His platelet count at the beginning of the study was  $159\,000/\text{mm}^3$ . Platelet count increased to  $100\,000/\text{mm}^3$  2 wk after drug discontinuation. Other laboratory tests did not show any significant change. Although nausea was seen in all patients, only three had severe vomiting that did not respond to symptomatic treatment and caused drug withdrawal. Among them, two had moderate HPS and one had severe HPS. No significant laboratory changes were seen in these patients. Treatment periods were 10 d, 28 d and 45 d. Other adverse effects did not cause drug withdrawal and improved with symptomatic treatment (two patients with fatigue and two with headache).

Among patients who completed the treatment period, average increment in PaO<sub>2</sub> was 26 mmHg and SaO<sub>2</sub> was 4.3%. At least 10 mmHg elevations in PaO<sub>2</sub> level was seen in all patients. Also, PaO<sub>2</sub> significantly decreased 3 mo after the end of treatment. Moreover, there was significant improvement in alveolar-arterial oxygen gradient at the end of the treatment period and a significant increase after drug discontinuation (Table 3). Among these patients, two had mild HPS and four had moderate HPS.

For clinical manifestations, there were no significant

**Table 3** PaO<sub>2</sub>, SaO<sub>2</sub> and alveolar-arterial oxygen gradient (A-a G) before, at the end and 3 mo after treatment among patients who could tolerate pentoxifylline (mean  $\pm$  SD)

Variables	PaO <sub>2</sub>	SaO <sub>2</sub>	A-a G
Baseline	73.3 $\pm$ 9.33	93.33 $\pm$ 6.28	40.10 $\pm$ 18.09
End of treatment	97.0 $\pm$ 3.79	97.66 $\pm$ 1.50	20.73 $\pm$ 9.46
Three months after treatment	71.83 $\pm$ 21.47	90.5 $\pm$ 8.6	43.68 $\pm$ 24.30
<i>P</i> value	0.02 <sup>1</sup> , 0.02 <sup>2</sup>	0.04 <sup>1</sup> , 0.05 <sup>2</sup>	0.02 <sup>1</sup> , 0.02 <sup>2</sup>

<sup>1</sup>Baseline *vs* end of treatment; <sup>2</sup>End of treatment *vs* 3 mo later. PaO<sub>2</sub>: Oxygen pressure; SaO<sub>2</sub>: Oxygen saturation.

change between baseline, the end of treatment, and 3 mo later. There was also no significant change in other laboratory tests. In a 12-mo period of follow-up after drug discontinuation, two patients died. The first was the 16-year-old boy with Wilson's disease. He died from upper gastroesophageal bleeding from esophageal varicose veins, 8 mo after drug withdrawal. The second was a girl of 2 years with cryptogenic cirrhosis who received PTX for 10 d. She was one of the three patients who could not tolerate PTX because of severe vomiting. She died due to hepatic encephalopathy and septicemia.

## DISCUSSION

In this pilot study, we found significant improvements in PaO<sub>2</sub>, SaO<sub>2</sub> and alveolar-arterial oxygen gradient after 3 mo therapy among patients who could tolerate PTX. PaO<sub>2</sub> was also significantly decreased at 3 mo after drug withdrawal, which supports the therapeutic effects of PTX. However, we did not find any significant change in clinical parameters. In this study, 40% of patients could not complete the treatment period. In other studies of patients with liver disease, drug withdrawal rate due to adverse effects ranged from 0% to 40%<sup>[17,21,22]</sup>. It seems that gastrointestinal intolerance was the most common cause (nausea in 100% and vomiting in 30%). Previously, animal studies have shown that inhibition of TNF $\alpha$  with PTX in cirrhotic rats after common bile duct ligation can improve HPS<sup>[23,24]</sup>.

Tanikella *et al*<sup>[25]</sup> selected nine adult patients with moderate to severe HPS. There was no significant difference in PaO<sub>2</sub> and alveolar-arterial oxygen gradient before and after PTX administration. High incidences of gastrointestinal adverse effects were the most important reason for intolerance. This resulted in a 44% attrition rate and only one patient (12%) could tolerate PTX for the complete treatment period of 8 wk.

Despite these results, Gupta *et al*<sup>[26]</sup> have demonstrated that 3 mo treatment with PTX can improve the symptoms and signs in about 90% of patients. There was also a significant increase in median supine, standing and postexercise PaO<sub>2</sub> ( $P < 0.01$ ). Side effects were reported in a few patients (vomiting in three and dyspnea in two), but they did not require drug withdrawal.

In our study, among the four patients who could not

tolerate PTX, two had moderate, one had severe and one had very severe HPS. Also, three patients had Child score C and one had Child score B. The high incidence of intolerance in these patients was comparable with that of the Tanikella *et al.*<sup>[25]</sup> study that was carried out in patients with moderate to severe HPS, and suggests that beginning PTX in the early stages of HPS may increase tolerability and effectiveness.

As far as we are aware, no study has determined the optimal dose of PTX in cirrhotic children. In animal studies, the dose of PTX used was 10-50 mg/kg per day<sup>[4,23,24]</sup>. PTX was used previously in children for treatment of Kawasaki disease as an antiplatelet drug with the same dose and no side effects were seen<sup>[27]</sup>. One potential explanation for this difference is significant first pass metabolism of PTX in the liver to an active metabolite, and consequently, serum levels are significantly high in liver dysfunction<sup>[28]</sup>. This problem does not occur in Kawasaki disease. Furthermore, finding the optimal dosage of PTX in liver dysfunction can be beneficial. In the present study, one patient experienced thrombocytopenia. Although thrombocytopenia is a manifestation of cirrhosis, decreased platelet count after administration of PTX, and increased platelet count after drug withdrawal denote the role of PTX. This implies that CBC is an important laboratory test during PTX administration. We did not observe any change in serum creatinine or liver function before and after therapy with pentoxifylline that may have contributed to changes in pentoxifylline metabolism.

To evaluate effects of PTX in HPS, we suggest double-blind studies, long-term treatment, and contrast echocardiography at the end of the treatment period for later studies. Meanwhile, it is necessary to evaluate optimal dose of PTX in cirrhotic children. In conclusion, it seems that PTX may have beneficial effects on oxygenation in early stages of HPS.

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## COMMENTS

### Background

Hepatopulmonary syndrome (HPS) is a triad of liver disease, arterial hypoxemia and widespread pulmonary vascular dilatation. There is currently no effective medical therapy for HPS in spite of several recommended medications. Recently, pentoxifylline (PTX), a nonspecific phosphodiesterase-4 inhibitor, which blocks tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) synthesis, has appeared to prevent HPS. The aim of this study was to evaluate the effect of PTX on clinical manifestations and arterial blood gas data in children with HPS.

### Research frontiers

This study, possibly for the first time, reported therapeutic effects of PTX in children with HPS. The authors concluded that there were no significant differences in clinical manifestations and other laboratory tests after treatment. PTX may improve arterial oxygen tension, oxygen saturation and alveolar-arterial oxygen gradient in the early stage of HPS. Thus, it seems that PTX may have beneficial effects on oxygenation in early stages of HPS.

## Innovations and breakthroughs

PTX, a nonspecific phosphodiesterase-4 inhibitor, blocks TNF $\alpha$  synthesis and seems to prevent HPS. The authors evaluated, perhaps for the first time, the therapeutic efficacy of PTX in children with HPS.

## Applications

The authors concluded that PTX may have beneficial effects on oxygenation in early stages of HPS. However, the authors suggest further double blind studies with longer treatment periods and contrast echocardiography at the end of the treatment period until the effect of PTX in HPS are defined clearly. Also, the authors recommend evaluation of the optimal dose of PTX in cirrhotic children.

## Peer review

This is a prospective study with a few patients. It is accepted with minor revisions.

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