Oral Tadalafil in Children with Pulmonary Arterial Hypertension

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Oral Tadalafil in Children with Pulmonary Arterial Hypertension

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Key words
- children
- pulmonary arterial hypertension
- phosphodiesterase type 5 (PDE-5) inhibitor
- tadalafil

Abstract

Objective: Tadalafil is a selective Phosphodiesterase-5 inhibitor that has been reported to have vasodilatory and antiproliferative effects on the pulmonary artery. In this study we evaluated the safety and efficacy of oral tadalafil in children with pulmonary arterial hypertension (PAH).

Methods: This open label study, prospective and interventional was carried out in 25 known patients aged 2 month–5 years in 3 medical centers in Iran, between March 2013–Jun 2014. Tadalafil suspension was administrated at 1 mg/kg daily for all patients. Hemodynamic and safety parameters were assessed at baseline and then monthly for a total of 4 visits.

Results: 19 patients received tadalafil as initial therapy, in all visits significant improvements in mean pulmonary arterial pressure were observed ($p<0.01$). Of the 25 patients, 6 (24%) had been on sildenafil for longer than 6 months. After transition from sildenafil to tadalafil clinical improvement was noted ($p<0.05$). Administration of tadalafil suspension was generally safe and well tolerated. Nausea was the most frequently reported adverse events which occurred in 3 patients during treatment.

Conclusions: Oral tadalafil was administered easily and tolerated well and improved mean pulmonary artery pressure (MPAP) in children with PAH, which suggests that oral tadalafil may be more effective and safer than sildenafil in the treatment of PAH.

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Introduction

Pulmonary arterial hypertension (PAH) is a group of diseases characterized by a progressive increase in pulmonary vascular resistance, leading to right ventricular failure and premature death [1,2]. PAH is usually defined as a chronic elevation of a mean pulmonary artery (PA) pressure above 25 mm Hg, measured invasively by a pulmonary artery catheter [3]. Without appropriate treatment, the natural history of PAH is progressive and fatal [4]. In recent years, significant advance in development and clinical implementation of a number of medications for PAH has been observed [5,6]. 2 important features of PAH are increased expression of the vasoconstrictor phosphodiesterases (PDE) and decreased production of the vasodilator nitric oxide in the pulmonary vasculature [7]. PDEs, as regulators of the second messenger response to endogenous NO, are thus of great therapeutic potential for the treatment of PAH [8]. PDE5 inhibitors have vasodilatory and antiproliferative effects on the pulmonary vasculature [7]. Tadalafil (Adcirca®), an orally administered, once-daily dosing, selective PDE5 inhibitor, is approved for the treatment of PAH [9]. Data on tadalafil for the treatment of PAH are limited and still now in children is not evaluated. Therefore, in this study we investigated efficacy and safety of tadalafil in children with PAH.

Material and Methods

Patients

Pediatric patients ≥2 months to <5 years of age with PAH, confirmed by echocardiography, who received conventional PAH medication on stable doses with no changes for at least 1 month before screening were included in the study. Exclusion criteria were as following: (1) current therapy with vasodilators, such as bosentan, epoprostanol; (2) severe hepatic impairment or renal

insufficiency; (3) currently receiving cancer therapy; (4) current use of CYP3A4 inhibitors or inducer drugs, such as ritonavir and other protease inhibitors, ketoconazole, itraconazole, erythromycin and rifampin.

Study design

The study was open label, prospective and interventional and performed between March 2013–Jun 2014 in 3 centers: Shafizade pediatric's Hospital in Amirkola, Avicenna pediatric's hospital in Sari and Tooba outpatient clinic in Sari, Mazandaran province, Iran. The study protocol was approved by the Research Ethics Committee of the Mazandaran University of Medical Sciences, Sari, Iran, and informed signed consent was obtained from the study subjects parents. All patients received tadalafil suspension at the dose of 1 mg/kg orally once per day. Hemodynamic parameters, by echocardiography, were measured at baseline and every month after starting tadalafil. Side effects and clinical worsening were used to assess safety and tolerability. Side effects such as headache, flushing, myalgia, peripheral edema, nasal congestion, nausea and diarihea were monitored at each clinic visit at every month intervals.

Statistical analysis

All the data were coded and SPSS 22 was used for the statistical analysis. The qualitative variables were presented by their frequency and percentage. The quantitative variables were summarized as mean ± standard deviation (SD). Continuous variables within groups before and after treatment were compared using a paired *t*-test and repeated measure ANOVA. A level of significance of 5% was chosen and all tests were two-sided.

Results

Patient population

25 patients (mean age 1.52 years) fulfilled entry criteria and were enrolled in the study protocol. The majority of patients were female (56%), and the diagnosis was persistent pulmonary hypertension in 3 of 25 (12%) patients, and 22 (78%) patients had associated CHD. All patients were on digoxin and captopril and one of them received spironolactone as part of their treatment. During the study, one patient was excluded because of diagnose of ALL after 2 months of taking tadalafil and one patient was missed during follow-up.

Table 1 shows the demographic and clinical characteristics of the study group.

Table 1 Demographic and clinical characteristics of the patients (n = 25).

Gender	Male	11 (44%)
	Female	14 (56%)
Age * (years)		1.52 (0.2–5)
Weight * (Kg)		9.40 (4–25)
	VSD + PH	7 (28%)
	VSD + PDA + PH	5 (20%)
Etiology	AVSD + PH	6 (24%)
	AVSD + PDA + PH	1 (4%)
	DORV + VSD + PH	3 (12%)
	PPHN	3 (12%)
	Digoxin	25 (100%)
Concomitant therapy	Captopril	25 (100%)
	Spironolactone	1 (4%)

* : Values are presented based on mean (range)

VSD = ventricular septal defect, AVSD = atrioventricular septal defect, PDA = patent ductus arteriosus, DORV = Double Outlet Right Ventricle, PPHN = Persistent pulmonary hypertension of the newborn

Transition from sildenafil to tadalafil

Of the 25 patients, 6 (24%) had been on sildenafil for longer than 6 months. At the time of transition, all of them were receiving oral sildenafil 1 mg/kg t.i.d. All of patients were successfully transitioned to tadalafil. Basal MPAP with sildenafil was 49.7 ± 8.8 mm Hg that significantly decreased with tadalafil oral suspension to 40.8 ± 13.9 mm Hg ($p < 0.05$) after 1 month, 39.2 ± 13.2 mm Hg ($p < 0.05$) after 2 months and MPAP fall to 35 ± 10.5 mm Hg ($p < 0.01$) at the end of the 3rd month use of tadalafil (**Fig. 1**).

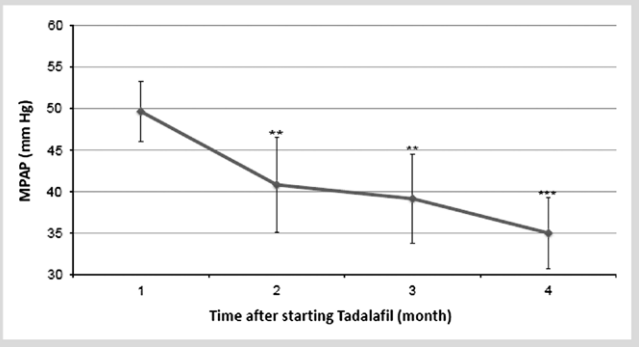

Fig. 1 Time course of mean pulmonary artery pressure (MPAP), after transition from sildenafil to tadalafil 1 mg/kg in 6 patients with pulmonary hypertension. * * $p < 0.05$, * * * $p < 0.01$ vs. baseline (n = 6).

Tadalafil as initial therapy

Tadalafil was started for 19 pediatric patients as initial therapy (76%). There was a significant decrease in MPAP after administration of oral tadalafil from 59.2 ± 12.8 mm Hg to 50 ± 14.5 mm Hg ($p < 0.01$) after one month, 45.5 ± 15.3 mm Hg ($p < 0.01$) and 39.4 ± 12.6 mm Hg (**Fig. 2**) ($p < 0.01$) after 2 and 3 months respectively.

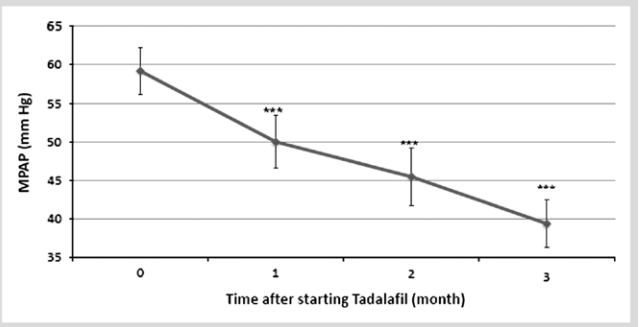

Fig. 2 Time course of mean pulmonary artery pressure (MPAP), after starting of treatment with tadalafil 1 mg/kg in 17 patients with pulmonary hypertension. * * $p < 0.05$, * * * $p < 0.01$ vs. baseline (n = 17).

Safety and tolerability

Administration of tadalafil suspension was generally safe and well tolerated (**Table 2**). Nausea was the most frequently reported AE, occurring in 12% of participants during treatment. Most of AEs were reported as mild in severity, and no serious AEs were reported. Of the 25 patients, 1 discontinued tadalafil due to nausea for 2 weeks; then tadalafil started again with dose

Table 2 Frequency and type of adverse effects observed following administration of oral tadalafil.

Type of AE	Frequency
Nausea	3
Flushing	2
Headache	2
Diarrhea	1
Nasal Congestion	1

of 0.5 mg/kg and gradually increased to 1 mg/kg within 2 weeks. One death occurred during the 3-month study and were not considered to be related to the tadalafil (end-stage PAH).

Discussion

This 3-month period study is the first analysis of the safety and efficacy of phosphodiesterase type 5 (PDE-5) inhibitor, tadalafil as initial therapy in pediatric with pulmonary arterial hypertension (PAH). Sildenafil and tadalafil are orally administered cyclic GMP (PDE-5) inhibitors that are indicated for the treatment of PAH. Several previous studies have demonstrated that sildenafil is effective on treatment of PAH in children and neonates [10–12]. In 2011, the results of STARTS-1, a 16 week randomized, double-blind, placebo-controlled sildenafil dose-ranging study in 235 children with PAH showed that that sildenafil monotherapy is well tolerated and improves hemodynamic, functional class and peak oxygen consumption parameters [13]. On August 2012, the FDA placed a safety warning on prescription of sildenafil in pediatric PAH patients, states that sildenafil should not be started in patients 1-17 years of age; based on increased mortality rate with high dose of sildenafil [14]. More recently FDA is clarified its previous recommendation and recognized some situations in which the benefit-risk profile of sildenafil may be acceptable in individual children, for example, when other treatment options are limited and sildenafil can be used with close monitoring [15]. Tadalafil, another selective PDE-5 inhibitor with longer-life of (17.5 h) when compared with sildenafil (4 h) may represent an attractive option to some patients especially in children as it may allow for less frequent dosing and a more sustained benefit and less dose-depended side effects.

The results of our study show that oral tadalafil (1 mg/kg once a day) improves hemodynamics (**Fig. 1,2**) as initial therapy or when administrated instead of sildenafil. Data about tadalafil effects on PAH are limited and our study was the first evaluation of this drug among pediatric patients. An initial report in 2004 by Palmieri et al. detailed the use of 20 mg tadalafil given every other day in a 72-year-old female patient with PAH who failed epoprostenol infusion; The patient ultimately showed improvements in hemodynamics (pulmonary artery systolic pressure by echocardiogram went from 105 mmHg at baseline to 65 mmHg 6 months later) [16]. The Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) trial randomly assigned 405 such patients to receive tadalafil (2.5, 10, 20, or 40 mg) or placebo once daily for 16 weeks; Improvements were observed with tadalafil 20 and 40 mg compared with baseline in mean pulmonary arterial pressure [17]. Ghofrani et al. have compared the hemodynamic effects of PDE5 inhibitors in the pulmonary and systemic vasculature of PAH patients for 120 min. All PDE5 inhibitors caused significant pulmonary vasodilation, but differed in the time for maximal effect and selectivity. Tadalafil showed maximal effect from 75 to 90 min (against 40–45 for vardenafil and 60 min for sildenafil). Tadalafil and sildenafil reported higher selectivity for pulmonary vasculature (reduction in pulmonary vascular resistance/systemic vascular resistance) [18]. Recently Zhuang et al. investigated whether adding tadalafil to existing ambrisentan is safe and effective in patients with PAH and reported that there were no significant differences in adverse events or changes in hemodynamic parameters between the placebo and tadalafil group [19]. The first report about safety and efficacy of tadalafil in pediatric PAH was published in 2013. In this study, 33 pediatric patients with pulmonary arterial hypertension were retrospectively evaluated. 29 of 33 patients were switched from sildenafil to tadalafil. The average dose of tadalafil was 1.0 ± 0.4 mg/kg/day. In 14 of 29 patients undergoing repeat catheterization, statistically significant improvements were observed following transition from sildenafil to tadalafil, in mean pulmonary arterial pressure (mmHg) (53.2 ± 18.3 vs. 47.4 ± 13.7, $p < 0.05$). 4 patients treated with tadalafil as initial therapy; due to the small number of the patients statistical analysis was not performed but similar to our results, clinical improvement was noted [20]. Also our results show a significant reduction in MPAP for each visit compared with previous visit in patient who received tadalafil as initial therapy ($p < 0.05$). This finding suggests that maximum effect of tadalafil on MPAP is achieved on long term and chronic use of tadalafil can be more effective.

We found that orally administered tadalafil as a once daily dosing drug was well tolerated in pediatric patients. Only 1 patient stopped tadalafil due to side effects including nausea. A small prospective study evaluating the feasibility of transitioning stable patients with PAH from sildenafil to tadalafil demonstrated that the transition was safe and generally well tolerated [21]. Recently Shapiro et al. assessed the feasibility of transitioning stable patients from sildenafil to tadalafil. Medical records from 98 patients were evaluated. Patient-reported adverse events included headache (4%) and heartburn (2%) and transition from sildenafil to tadalafil 40 mg/day appeared feasible without clinical deterioration or intolerable side effects [22]. Also Takatsuki et al. study showed that the side effect profiles of tadalafil initial therapy were similar for the patients who had transitioned from sildenafil to tadalafil including headache, nausea, myalgia, nasal congestion, flushing, and allergic reaction; 2 patients discontinued tadalafil due to migraine or allergic reaction and one patient receiving sildenafil had no breakthrough syncope after transition to tadalafil [20]. Results of another study that was carried out in 18 PAH patients aged 4–24 years in Iran, showed the echocardiographic changes while taking the sildenafil or tadalafil were not significantly different. Also frequency of development of adverse effects after taking sildenafil and tadalafil did not significantly differ in this study [23].

In conclusion, the favorable effects of tadalafil therapy on hemodynamics in treatment of PAH in children and the relatively low cost, side effects and longer half-life with one single administration every day of this medication suggest its usefulness as a first-line treatment insisted of sildenafil in developing countries.

Conflict of Interest

The authors declare no conflicts of interest.

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