Pediatr Cardiol (2014) 35:490–498
DOI 10.1007/s00246-013-0811-4

ORIGINAL ARTICLE

Safety and Tolerability of Targeted Therapies for Pulmonary Hypertension in Children

T. Roldan · L. Deiros · J. A. Romero · F. Gutierrez-Larraya · A. Herrero · M. J. Del Cerro

Received: 21 July 2013 / Accepted: 24 September 2013 / Published online: 20 October 2013

Abstract The objective of this study is to evaluate the safety and tolerability of the pharmacological treatment of pulmonary hypertension in pediatric patients. It is a retrospective, longitudinal, observational study on pediatric patients undergoing treatment with pulmonary targeted therapies. 63 patients were included (51 % male), with a median age of 3.4 years (IQR, 3.6 months–10 years) and a median weight 13 kg (IQR, 6–30 kg). Congenital heart disease was the etiology of pulmonary hypertension in the majority of cases ($n = 33$) and 28 patients were in NYHA functional class III–IV. The most commonly used drug was sildenafil ($n = 79$, 56 %), followed by bosentan ($n = 27$, 23 %), and a combination of both ($n = 14$, 41 %). 34 patients had adverse reactions (54 %) with an incidence rate of 1.02 per patient per year. The most commonly reported reactions were gastrointestinal symptoms (22 %) and spontaneous erections (22 %) in males. Nine severe adverse reactions (10 %) occurred, requiring eight treatment withdrawal and one hospital admission. Treatment with targeted therapies for pulmonary hypertension is safe in the pediatric population. Severe ADRs were uncommon both in monotherapy and in combination therapy. Combination therapy was associated with a higher rate of ADRs. We observed similar survival rates in children receiving sildenafil doses according to the European Medicines Agency (EMA) recommendations or higher.

T. Roldan · J. A. Romero · A. Herrero
Department of Pharmacy, Hospital Universitario La Paz, Madrid, Spain

L. Deiros · F. Gutierrez-Larraya · M. J. Del Cerro (✉)
Pediatric Pulmonary Hypertension Unit, Department of Pediatric Cardiology, Hospital Universitario La Paz, Madrid, Spain
e-mail: mjesus.cerro@salud.madrid.org

Keywords Pulmonary hypertension · Pediatrics · Pharmacotherapy · Safety

Introduction

Pulmonary hypertensive vascular disease (PHVD) is a pathophysiological condition defined by an increase of mean pulmonary artery pressure, and it has been classified into five different etiopathogenic groups [21]. Nevertheless, pulmonary hypertension (PH) is heterogeneous and often multifactorial condition in children [9]. Recently, specific classifications for PHVD [10], epidemiologic data (the United Kingdom registry, Dutch registry and REVEAL registry) [4, 12, 24] and pharmacotherapy advances have been published [18]. Of the available drugs for pulmonary arterial hypertension (PAH), sildenafil has been approved for use in children in Europe but not in the United States, and bosentan, although not yet officially approved in Europe or the United States, has been widely used in both regions. Furthermore, there was a recent warning against the use of high doses of sildenafil in children, and in August 2012, the United States Food and Drug Administration issued a safety alert against the use of sildenafil in children 1–17 years old. Therefore, there is a need for more information regarding the safety and tolerability of these drugs in children, especially when these drugs are used in combination. Childhood constitutes a period of human development characterized by a series of physiological, therapeutic and pharmacological circumstances that render newborns and children particularly vulnerable and sensitive to adverse drug reactions (ADRs). As a result, the adverse effects of pulmonary vasodilator drugs observed in adults cannot be extrapolated to the pediatric population because they can vary in incidence, effect and severity.

The primary objectives of our study were to evaluate the safety and tolerability of PHVD targeted therapies in children (including in combination therapy) and analyze the incidence and type of ADRs in our pediatric population. Our secondary objectives were to study the possible risk factors associated with these ADRs in children, to compare ADRs described in the adult population to those detected in the pediatric population, and to study possible differences in survival according to sildenafil dosing.

Materials and Methods

This was a retrospective, longitudinal, observational study of a series of cases from a single center. We included 63 pediatric patients with PHVD, confirmed by catheterization, who were diagnosed and followed-up in our outpatient clinic from January 2006 to February 2011 and who received treatment with any of the following pulmonary vasodilators: sildenafil, bosentan, iloprost, treprostinil, epoprostenol, ambrisentan, and sitaxentan. The median and interquartile range (IQR) length of follow-up for ADRs was 12 months (range 5–9) from the start of therapy to February 2011. To evaluate possible differences in survival between patients receiving sildenafil doses equal to or greater then European Medicines Agency (EMA) recommendations, we extended the follow-up for survival to December 2012. The median and IQR follow-up for survival was 2.6 years (range 1–3.5). The regular follow-up visits included systematic inquiry about possible ADRs. Through retrospective chart review, we collected patient demographics, including sex, age, diagnosis, etiology, and New York Heart Association (NYHA) functional class (Table 1), as well as drug therapy variables—e.g., dose, regimen, duration, and other associated drugs—along with variables related to possible adverse events detected, such as description, severity, physician process, and Naranjo algorithm score [17]. Naranjo algorithm score was calculated for all of the pulmonary vasodilator drugs used in monotherapy. In the case of combined therapy, it was only applied for drugs in which the mechanism of action of one of them could justify a suspected ADR. Possible ADRs detected were checked on the Drug Summary of Medicinal Product Characteristics (SPC) [11, 19, 20, 22, 23, 25, 26], to distinguish among possible ADRs and symptoms or signs of disease and to estimate the cause–effect relationship based on the score obtained from the Naranjo algorithm. ADRs were considered to be those with a score ≥ 1. Any suspected ADRs that surpassed any of the above-mentioned three requirements on evaluation were categorized as ADRs. The incidence rate of ADR per patient-year was calculated using the total ADRs observed and the sum of the person-time of the risk population as the denominator (different length of follow-up in each patient). In parallel, the safety assessment for using two or more associated pulmonary vasodilator drugs consisted of studying the correlation between the number of ADRs and the number of pulmonary vasodilators administered as well as comparing the number of ADRs from one pulmonary vasodilator with the number of ADRs associated with combined therapy. Sildenafil, the drug most commonly used in both monotherapy and in combination, was used as the reference drug against which to compare the number of ADRs.

Table 1 Baseline characteristics of the pediatric patients ($n = 63$)

Baseline characteristics	No. of patients (%)
Sex	
Male-to-female ratio	32/31 (1.03)
Age (years) (%)	
≤2	27 (42.9)
2–8	13 (20.6)
≥8	22 (34.9)
Diagnostic group (based on Dana Point classification; %)	
Group I: Pulmonary arterial hypertension	39 (61.9)
Congenital heart disease	33 (52.4)
IPAH	5 (7.9)
PoPH	1 (1.6)
Group II: Left heart disease	2 (3.2)
Group III: Lung disease/hypoxemia	12 (19)
BPD	4 (6.3)
Other lung diseases	8 (12.7)
Group V: Metabolic diseases	3 (4.8)
Others: High PVR in Fontan patients	7 (11.1)
NYHA functional class (%)	
I	1 (1.6)
II	14 (22.2)
III	25 (39.7)
IV	23 (36.5)

IPAH idiopathic pulmonary arterial hypertension; *PoPH* portopulmonary hypertension; *BPD* bronchopulmonary dysplasia; *PVR* pulmonary vascular resistance

We also studied possible risk factors that might increase susceptibility to ADRs, including patient characteristics (age, sex, etiology, and severity of the disease) and drug dose. Adverse effects in the adult and pediatric populations were compared using the ADR frequency data collected from the drug SPC for adults and the calculated values for our study pediatric population. We retrospectively analyzed the possible relationship between adverse effects and mortality according to sildenafil dosing in our group of patients.

To describe continuous variables, we used medians with IQRs and the means with SDs. Qualitative variables were described using absolute numbers and relative frequencies expressed as percentages. Comparisons between quantitative and qualitative variables were primarily performed using Kruskall–Wallis or Mann–Whitney U nonparametric

test. Analyses between qualitative variables were performed using chi-square test or Fisher's exact test when necessary. When chi-square test was used, Yates correction was applied in all cases. The correlation between quantitative variables was determined using Spearman's rank correlation coefficient. The level of statistical significance was established at $p < 0.05$. Kaplan–Meier survival estimates (±SE) from the start of therapy were calculated for the whole cohort; *p*-values were obtained using log-rank; and *p*-values were calculated for hazard ratios for sildenafil dosing according to SPC recommendations versus sildenafil doses greater than SPC recommendations using Cox proportional hazard models.

Results

Demographic and Baseline Characteristics

Sixty-three pediatric patients were included in the study, in whom a total of 90 different treatment regimens (monotherapy and combination) were analyzed. The median age at the start of therapy was 3.4 years (IQR 3.6 months–10 years), and the median weight was 13 kg (IQR 6–30). The male-to-female ratio was 1.03, and the etiology of PHVD and NYHA functional class are listed in Table 1. Sildenafil was used in 69 patients (58 %) with a median dose of 3.6 mg/kg/d (range 0.9–7.9), bosentan in 27 patients (23 %) at 2 mg/kg/12 hours, iloprost in 12 patients (10 %) at 10 mcg/kg/dose (range 4–20), treprostinil in 10 patients (8 %) at 22.5 ng/kg/min (range 12–34), and ambrisentan (2.5 mg once daily), sitaxentan (2 mg/kg/12 h), and epoprostenol (20–40 ng/kg/min) in one patient each (1 %). The description and frequency of the combined treatments are shown in Fig. 1. All of the patients receiving bosentan underwent monthly liver function testing.

Safety Variables Associated With Treatment

Of the 63 studied pediatric patients, 34 (54.0 %) had ADRs. A total of 90 episodes were recorded, 37 with monotherapy treatment and 53 with combined therapy, for an overall incidence rate of 1.02 ADRs/patient/year. 25 different ADRs were detected (22 related to the drug and three related to the route of administration), as listed in Table 2, with the following cause–effect relationships resulting from the application of the Naranjo algorithm: possible (score of 1–4) = 25.5 %, probable (score of 5–8) = 48.9 %, definite (score ≥ 9) = 5.6 %, and undetermined (score not calculated) = 20.0 %.

ADRs that were most frequently observed in the pediatric population in the present study were gastrointestinal symptoms in 14 patients (22.2 %) and spontaneous erections in seven male patients (21.9 %). Occurring in order of decreasing frequency were the following: headache ($n = 7$, 11.1 %), hemorrhagic diathesis ($n = 6$, 9.5 %), and facial flushing ($n = 6$, 9.5 %). A large number of patients presented ADRs associated with the route of administration, most commonly inhaled ($n = 7$, 63.6 %) and subcutaneous ($n = 5$, 55.6 %). The only patient who received intravenous epoprostenol developed catheter-related sepsis (Table 2).

Eighty-three of the 90 ADRs recorded were related to the mechanism of action of the drugs (type A), and seven were idiosyncratic (type B). ADRs directly attributed to the mechanism of action and/or the route of administration were the following: vasodilatation-mediated in 45 (54.2 %), gastrointestinal symptoms in 17 (20.5 %), route of administration in 14 (16.9 %), and prostacyclin (PC) actions in 9 of 83 type A ADRs (10.8 %). Among the idiosyncratic ADRs, there was 1 case of increased hepatic transaminases 2–4 times greater than the upper limit of normal with bosentan.

ADRs were classified as mild in 42 (46.7 %), moderate in 39 (43.3 %), and severe in nine (10.0 %) cases. Of the nine severe ADRs, three occurred in patients taking monotherapy and six in patients using combined therapy. In 59 ADRs, treatment was not changed (64.8 %), whereas in 18 (26.0 %) the dose was decreased, and treatment was stopped in eight ADRs (11.9 %). Sildenafil was the drug that needed to be decreased most often due to its associated ADRs. Bosentan was increased once, and no ADRs

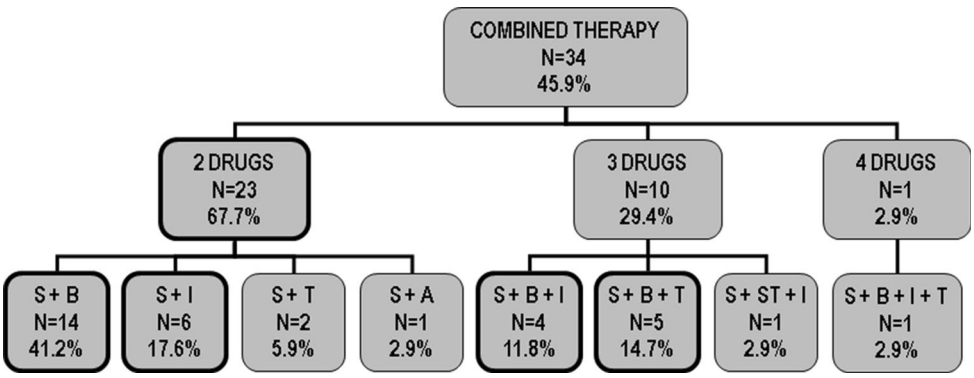

Fig. 1 Description of the combined treatments used in the study patients

Table 2 Table of ADRs detected in pediatric patients expressed as the number of treatments before each ADR and number of patients who each had ADR

ADR detected	No. of treatments with each ADR ($n = 90$)	No. of patients with each ADR ($n = 63$)	Type	Mechanism of production	Naranjo category/ median (range) score
Gastrointestinal symptoms (%)	17 (18.9)	14 (22.2)	A	Gastrointestinal disorders	Possible; 4 (3–10)
Headaches (%)	9 (10.0)	7 (11.1)	A	Vasodilation	Probable; 5 (1–5)
Spontaneous erections[a] (%)	7 (19.4)	7 (21.9)	A	Vasodilation	Probable; 7 (6–11)
Hemorrhagic diathesis (%)	6 (6.7)	6 (9.5)	A	Vasodilation, PC effect	Probable; 6 (3–6)
Facial flushing (%)	6 (6.7)	6 (9.5)	A	Vasodilation	Probable; 5.5 (5–6)
Nasal congestion (%)	5 (5.6)	5 (7.9)	A	Vasodilation	Probable; 5 (2–7)
Dizziness (%)	3 (3.3)	3 (4.8)	A	Vasodilation	Possible; 3 (2–4)
Vision problems (%)	3 (3.3)	3 (4.8)	A	Other mechanisms	Probable; 7 (6–7)
Increased secretions (%)	2 (2.2)	2 (3.2)	A	Vasodilation	Probable; 5 (4–6)
Decrease oxygen saturation (%)	2 (2.2)	2 (3.2)	B	Other mechanisms	Probable; 5
Fever (%)	2 (2.2)	2 (3.2)	A	Vasodilation	Possible; 2
Hematomas (%)	2 (2.2)	2 (3.2)	A	PC effect	Probable; 6.5 (6–7)
Hypotension (%)	2 (2.2)	2 (3.2)	A	Vasodilation	–
Irritability (%)	2 (2.2)	2 (3.2)	B	Other mechanisms	Possible; 3
Skin changes (%)	1 (1.1)	1 (1.6)	B	Other mechanisms	Possible; 3
Dilutional anemia (%)	1 (1.1)	1 (1.6)	A	Vasodilation	Possible; 4
Increased transaminases (%)	1 (1.1)	1 (1.6)	A	Other mechanisms	Probable; 7
Pain in limbs (%)	1 (1.1)	1 (1.6)	B	Other mechanisms	Probable; 5
Jaw pain (%)	1 (1.1)	1 (1.6)	A	PC effect	Probable; 5
Edemas (%)	1 (1.1)	1 (1.6)	A	Vasodilation	Possible; 3
Palpitations (%)	1 (1.1)	1 (1.6)	A	Vasodilation	–
Tremors	1 (1.1)	1 (1.6)	B	Other mechanisms	Probable; 7
Complications from the route of administration					
Administration by inhalation (cough, bronchospasm, facial erythema) (%)	8 (66.7)	7 (63.3)	A	Aerosol inhalation	Probable; 6.5 (6–8)
Subcutaneous administration (infusion site pain, arm edema) (%)	5 (50.0)	5 (55.6)	A	Unknown	Probable; 8 (6–11)
Intravenous administration (sepsis) (%)	1 (100)	1 (100)	A	Catheter-related complications	Probable; 8

[a] For spontaneous erections, only the male subjects in the population were considered. $n = 36$ in the number of prescribed treatments, and $n = 32$ in the number of patients

required discontinuation. In contrast, five ADRs required treatment (7.4 %). Acetaminophen for headaches and infusion site pain, salbutamol for bronchospasm, and ranitidine or domperidone for gastroesophageal reflux (GERD) were administered. It should be noted that due to the subcutaneous administration of treprostinil, one of the patients had a severe episode of edema on the injection arm requiring hospital admission and treatment withdrawal. Another two patients who presented episodes of edema and local pain did not require inpatient treatment.

We did not find any statistically significant relationships between sex or etiology and frequency of ADRs. ADRs were more common in patients with advanced NYHA functional classes, but the difference was not significant. In general, more ADRs were detected with advancing age; however, the differences between the average ADRs per

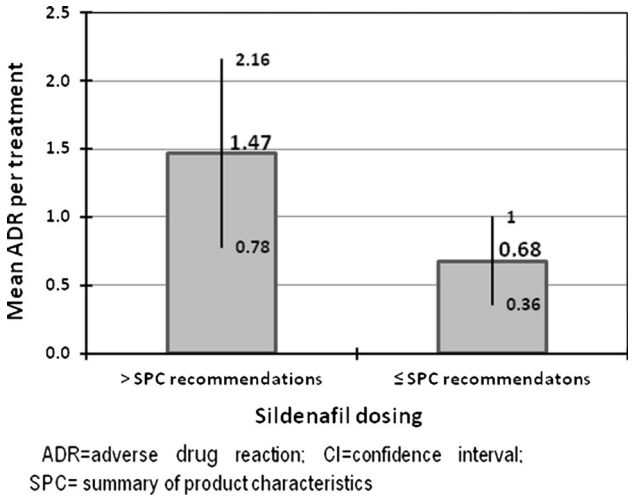

Fig. 2 ADR comparison according to adherence to summary of medicinal product characteristics (SPC)

prescribed treatment according to age groups were not statistically significant. There was a statistically significant increase in the incidence of headache with advancing age ($p < 0.05$). Two episodes developed in patients between 2 and 8 years of age (13.3 %) and seven in those >8 years of age(24.1 %). Fewer gastrointestinal symptoms were observed in children >2 years old than in those younger than this age (31.0 % vs. 43.6 %), but the difference was not statistically significant.

Regarding the possible relationship between adverse effects and sildenafil dosing, we detected a statistically significant increase in the number of ADRs when the sildenafil dose was greater than SPC recommendations (10 mg/8 h for patients weighing <20 kg and 20 mg/8 h for those weighing >20 kg) (Fig. 2). In particular, the increase in episodes of headache and hemorrhagic diatheses in this group of patients was statistically significant. No patients receiving the SPC-recommended doses of sildenafil had either of these two ADRs compared with seven episodes of headache (23.3 %) and six (20.0 %) of hemorrhagic diathesis in the group of patients receiving greater doses of this drug. A comparison between ADRs reported in SPCs for the adult population and ADRs encountered in our pediatric population is listed in Table 3.

Combined Therapy

We found a positive, statistically significant correlation between the number of drugs used and the ADRs described. Spearman's rank correlation coefficient of the curve obtained had a value of $r = 0.239$. The mean of ADRs was greater in combined therapy compared with monotherapy (1.53 ADR, SD = 1.50 vs. 0.93 ADR, SD = 1.07). The differences found were statistically significant. The specific ADRs with sildenafil monotherapy versus combination therapy, including sildenafil, are listed in Table 4.

Table 3 Comparison between adult ADR frequencies reported in SPCs and pediatric ADR frequencies found in the present study

Drug/ADR	Adult population (%)	Pediatric group (%)
Sildenafil		
Respiratory disorders (nosebleed, cough, nasal congestion)	1–10	18
Gastrointestinal symptoms		
Diarrhea and vomiting	≥10	18
Gastro-esophageal reflux and abdominal pain	1–10	15
CNS disorders		
Headaches	≥10	13
Tremors	1–10	2
Erections	UK	12
Facial flushing	≥10	10
Eye disorders	1–10	5
Dizziness	1–10	5
Psychiatric disorders (irritability)	1–10	3
General disorders (pyrexia)	1–10	3
Skin disorders	UK	2
Pain in limbs	≥10	2
Edemas	1–10	2
Bosentan		
Vascular disorders (hypotension and facial flushing)	1–10	20
CNS disorders (headaches)	≥10	16
Increased transaminases	≥10	4
Cardiac disorders (palpitations)	1–10	4
Anemia	1–10	4
Iloprost		
Respiratory disorders		
Cough	≥10	36
Bronchospasm	UK	9
Vascular disorders (hypotension, vasodilation)	≥10	36
Increased secretions	UK	18
CNS disorders (headaches)	1–10	9
Jaw pain	1–10	9
Treprostinil		
Complications from the route of administration	85	56
Headaches	27	22
Hematomas	20	22

CNS central nervous system, *UK* unknown

Table 4 Number and frequency of ADRs in patients receiving different therapeutic regimens

ADRs	Sildenafil ($n = 35$)	Sildenafil + bosentan ($n = 14$)	Sildenafil + bosentan + prostacyclin ($n = 10$)
Vasodilatation	14/35	12/14	6/10
Headaches	3/35	3/14	2/10
Hemorrhagic diathesis	3/35	1/14	2/10
Facial flushing	1/35	3/14	2/10
Gastrointestinal symptoms	9/35	1/14	2/10
Erections[a]	5/16	1/9	1/6

[a] For spontaneous erections, only the male subjects in the population were considered

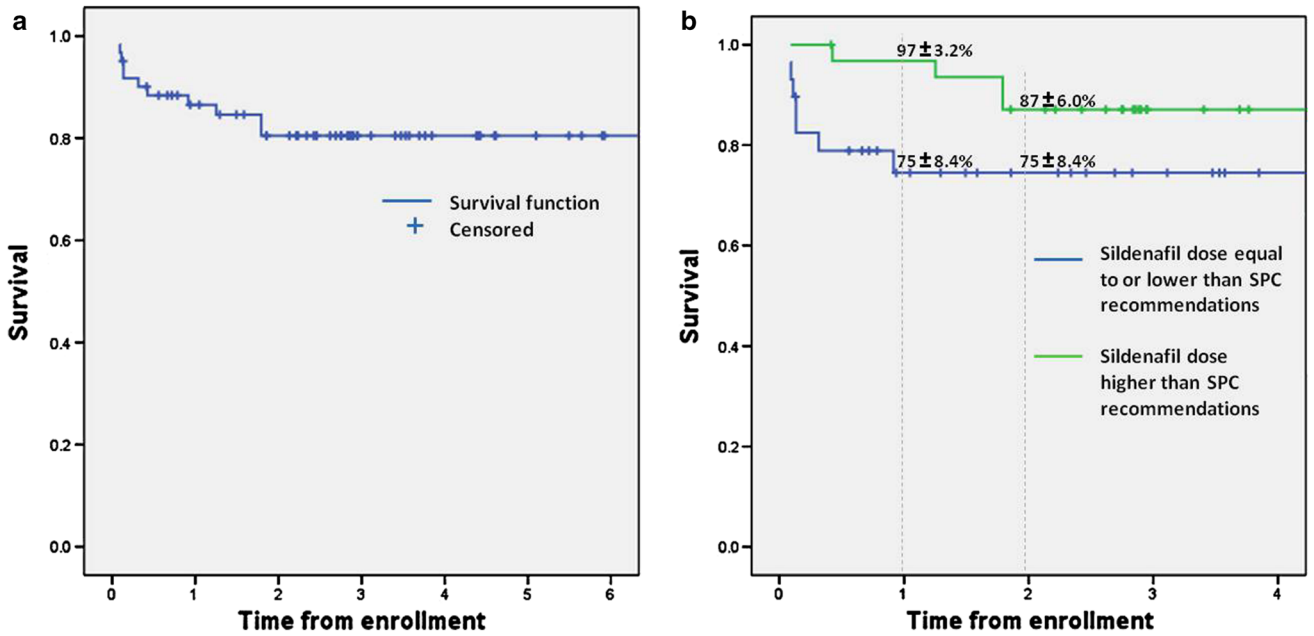

Fig. 3 Kaplan–Meier estimated survival from the start of sildenafil therapy **a** in the whole cohort and **b** according to sildenafil dosing

Outcomes

The survival rates for the entire cohort were 86.5, 80.5, and 80.5 % at 1, 2, and 3 years of follow-up (Fig. 3a), respectively. We had 29 (47.5 %) patients receiving sildenafil doses equal to or less than SPC recommendations and 32 (52.5 %) patients receiving doses greater than SPC recommendations. We did not find statistically significant differences in survival between these two groups of patients (Fig. 3b). There were also no differences in survival among patients on sildenafil monotherapy ($n = 35$) according to sildenafil dosing (doses of EMA recommendations or greater). There was a significant ($p < 0.05$) trend toward increased mortality in patients <2 years old with all of the deaths occurring in patients weighing <20 kg.

Discussion

PAH treatment was initiated in advanced NYHA functional classes in the majority of patients. The most commonly used drug in our study was sildenafil (both as monotherapy and as combination therapy). Prostanoids were used primarily in patients in advanced NYHA functional classes. None of the patients who died had indications for intravenous prostanoids; in three of them, limitation of therapeutic effort was applied due to multiorgan failure, comorbidities due to PH, and ethical issues. The only patient who received sitaxentan had just started the treatment 1 month before the withdrawal of this drug from the market.

Incidence and Characterization of ADRs

Although more than half of the study population had an ADR, the overall incidence rate was relatively low, with approximately one ADR/patient/treatment year. Given that the majority of the ADRs record were of a mild-to-moderate nature, with dose adjustment required in only 26.9 % of cases, and considering the life-threatening character of PAH, these therapies can be considered to have an acceptable safety profile in the pediatric population.

The majority of the ADRs produced in the patients studied were headaches, spontaneous erections, and facial flushing due to the vasodilator effects of the drugs used in the study; gastrointestinal alterations (GERD, diarrhea, abdominal distension, nausea and vomiting) were also frequent and were most commonly associated with sildenafil use.

After applying the Naranjo algorithm, the results obtained showed a consistent relationship between the drugs administered and the ADRs produced. The ADRs considered probable or definite (score > 5) constituted more than half of the total episodes evaluated. Nevertheless, due to the retrospective nature of the study, a cause–effect relationship could not be definitely established in many cases.

Severe ADRs requiring treatment discontinuation or a dose decrease were uncommon: There was one case of severe edema and pain at the infusion site of treprostinil needing hospital admission. one episode of sepsis after intravenous administration of epoprostenol, severe gastrointestinal symptoms (vomiting and diarrhea) associated with sildenafil, bosentan, or iloprost ($n = 7$), and priapism with sildenafil ($n = 2$). A single episode of increase in hepatic enzymes occurred in a 10-month-old patient, which resolved after decreasing the dose of bosentan. The frequency of this ADR in pediatric patients treated with bosentan (1.6 %) was less than that reported in the literature at 2.7 % in patients between 2 and 11 years of age and 7.8 % in patients >12 years old [7].

Risk Factors for ADRs

We found a different pattern and incidence of ADRs in the each of the age groups. There was a nonsignificant increase in the incidence of ADRs in children >8 years old (Fig. 3). In children <2 years old, gastrointestinal symptoms were more frequent, whereas headaches were more common in children >8 years old. This increase could be explained by the greater doses prescribed based on the weight of the patients or by the improvement in communication skills that is acquired during maturation. The statistically significant increase in headaches with age coincides with that described in the literature because the prevalence of all childhood headaches increases with age [14]. Unlike headaches, it appears that digestive symptoms follow an opposite tendency, i.e., decreasing as patient age. The absence of statistical significance shown by this hypothesis can be explained by the limited number of patients. The ADRs detected that were considered to be gastrointestinal symptoms included GERD, diarrhea, and nausea and vomiting. All of these ADRs have signs that can be easily noted by a doctor or the guardian of the pediatric patient and can be detected at any age. The most frequent disorder in pediatric patients of a younger age was GERD, which coincides with drug therapies based mainly on sildenafil in monotherapy. Sildenafil is capable of producing GERD due to the relaxation of the esophageal sphincter and the smooth muscle tissue [15]. This result is not unanticipated given that the efficacy of the antireflux system is limited in newborns and infants due to a lack of maturity [1]. The nonsignificant increase in ADRs as the severity of disease increases was likely due to the increasing use of combined treatment in the patients in advanced NYHA functional classes according to the recommendations of pharmacotherapeutic guidelines [3, 8].

Comparison of ADRs in Pediatric versus Adult Populations

Although the type of ADRs identified in this pediatric population were similar to those described in the adult population, the frequency of specific ADRs was different; such a comparison for every targeted PH drug has not been undertaken before. The most notable differences in the frequency of specific ADRs for every individual drug were as follows. For sildenafil, erections are not included in the drug SPC, whereas in our study we observed a considerable number of this ADR in the pediatric population. This finding is also coincident with the reported data from the STARTS–1 clinical trial [5] and is justified by the mechanism of action of the drug itself. The frequency of limb pain observed was slightly lower than that established for the adult population. This different might be due to difficulty in the etiological identification of this ADR, which can cause it to be confused with the symptomatology of the disease itself. For bosentan, the most notable ADR was a significant increase in vascular disorders (hypotension and facial flushing), which were twice as common in the pediatric population compared with adults. These data might have been influenced by the drug in our study having mainly been administered in combination with another vasodilator, which would have strengthened its effects on a vascular level. Regarding the increase in transaminases, the frequency of this ADR was much lower than that observed in adults (presenting in only one patient) [7]. For iloprost, the most significant differences observed were the greater incidence of broncho-constriction and an increase in secretions in the pediatric population. These ADRs could be explained by the greater reactivity and lower size of children's airways and by some of the children receiving iloprost with different nebulizers and others receiving it during mechanical ventilation. For treprostinil, the most common side effect in the adult population is local pain, which can cause treatment withdrawal in ≤23 % of adults [2]. In our patients, only 10 % of the pediatric patients receiving this drug did not tolerate it due to local reactions, which is concordant with other published data [16]. In contrast, the incidence of bruising and bleeding in our

patients (22 %) was similar to the rate reported in adults (20 %) [2].

ADRs in Combined Therapy

There has been lack of data in the literature regarding the incidence and profiles of ADRs in children receiving PH-targeted drugs in combination therapy. Therefore, this study provides new information about the safety of several of these combination regimens in the pediatric population. The results obtained showed a statistically significantly positive correlation between the use of combined therapy and the number of ADRs. This result might be due to the synergistic effects of the drugs, with half of patients receiving triple pharmacological therapy and presenting adverse reactions. This fact could also explain the greater percentage of severe ADRs in children receiving combined treatment than in children using monotherapy in our study and in adults as well (6.8 %) [13]. The high percentage of patients receiving combined therapy in this study was related to advanced NYHA functional class; although there is a lack of scientific evidence and guidelines about the indications of combined therapy in children, our Pediatric PH Unit used a "goal-oriented" treatment algorithm. The underlying diagnosis, associated comorbidities, and/or young age limited the prescription of parenteral prostanoids in some of the patients in NYHA functional class IV.

Given that sildenafil was the drug most commonly used in combination therapy, we performed a more detailed analysis. In the combination of sildenafil and bosentan, we observed a greater incidence of vasodilatation-related ADRs (headaches, hemorrhagic diathesis, and facial flushing). Possibly due to the pharmacokinetic interaction between the two drugs [5], some sildenafil-related ADRs (erections and gastrointestinal symptoms) were less common when the drug was used in combination with bosentan. Bosentan induces the metabolism of sildenafil, resulting in a less favorable balance for the specific effects of sildenafil due to a decrease in its plasma concentrations.

In summary, strict monitoring of combined treatment is recommended given the variability observed in ADRs with different pharmacological combinations, especially for treatments in which sildenafil and bosentan are involved.

Sildenafil Dosing and Survival Outcomes

The results of the STARTS-2 trial [5, 6], showing worse survival in children receiving high doses of sildenafil in monotherapy, caused the EMA to issue a warning against the use of high doses of sildenafil and the USFDA to recommend against the use of sildenafil in children. In our study, sildenafil dosing was in accordance with EMA recommendations (10 mg/8 h for patients weighing <20 kg and 20 mg/8 h for those weighing >20 kg) in 47.5 % of patients. There was a statistically significant increase in ADR frequency in patients receiving greater doses than recommended. The STARTS-2 trial found an unexplained increase in the incidence of death in patients receiving high doses of sildenafil compared with those receiving low or medium doses [6]. In our retrospective study, the use of sildenafil at doses greater than recommended was not associated with lower survival rates.

The greatest mortality observed was in patients <2 years old regardless of the sildenafil dose received. This result might have been due to the severity and etiologies of PHVD disease in this group of patients. Nevertheless, comparing the survival rates between our patients and STARTS-2 trial patients would be complicated because of the striking differences in age and PHVD etiologies as well as the fact that almost half of our patients received combined therapy.

Conclusion

1. In this retrospective study, the treatment of children with specific drug therapies for PHVD was safe, and although the incidence of ADRs was high, severe ADRs were uncommon both in monotherapy and in combination therapy.
2. The most significant risk factor for ADRs with PHVD-specific drugs in children was combination therapy, which was associated with a greater rate of ADRs. The age of the patients was related to the type and frequency of specific ADRs.
3. We observed similar survival rates in children receiving sildenafil doses at EMA recommendations or greater both in sildenafil monotherapy and in combination. Although this was a small cohort, our results are in discordance with the STARTS-2 findings.

Study Limitations

PH is a rare disease, and although this is the largest pediatric cohort reported to date to examine ADRs specifically, both in monotherapy and combination therapy, the study population was still small. The small number of patients included is the main limitation of this study. Although the clinical visits included specific inquiries about possible ADRs, the retrospective nature of the study is another limitation of this study.

Acknowledgments The authors thank all of their colleagues who participated in this study for their valuable comments and ideas, particularly Villamañán Bueno, Larrubia Marfil, and Perez Robles. Thanks also to Amber Castle from the Pharmacy Department of Yale–New Haven Hospital and Erica Wagner from the University of Wisconsin–Madison School of Pharmacy for their critical review of the first draft of this article and to the Biostatistics Section of IdiPAZ Institute for the statistical analysis. Translation into English was financed by Pfizer.

References

1. Armas H, Ortigosa L (2008) Reflujo gastroesofágico y esofagitis en niños. In: SEGHNP (ed) Tratamiento en gastroenterología, hepatología y nutrición pediátrica. Ergon, Madrid, pp 92–94
2. Barst RJ, Galie N, Naeije R, Simonneau G, Jeffs R, Arneson C, Rubin LJ (2006) Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil. Eur Respir J 28(6):1195–1203
3. Barst RJ, Gibbs JS, Ghofrani HA, Hoeper MM, McLaughlin VV, Rubin LJ, Sitbon O, Tapson VF, Galiè N (2009) Updated evidence-based treatment algorithm in pulmonary arterial hypertension. J Am Coll Cardiol 54(1 Suppl):S78–S84
4. Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD (2012) Survival in childhood pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Circulation 125(1):113–122
5. Barst RJ, Ivy DD, Gaitan G, Szatmari A, Rudzinski A, Garcia AE, Sastry BK, Pulido T, Layton GR, Serdarevic-Pehar M, Wessel DL (2012) A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension. Circulation 125(2):324–334
6. Barst RJ, Layton Jr, Konourina I, Richardson H, Beguetti M, Ivy DD (2012) Starts-2: Long term survival with oral sildenafil monotherapy in treatment-naive patients with pediatric pulmonary arterial hypertension. Abstract presented at the European Society of Cardiology meeting, Munich, 25–29 August 2012
7. Beghetti M, Hoeper MM, Kiely DG, Carlsen J, Schwierin B, Segal ES, Humbert M (2008) Safety experience with bosentan in 146 children 2–11 years old with pulmonary arterial hypertension: results from the European postmarketing surveillance program. Pediatr Res 64(2):200–204
8. Berger RM, Bonnet D (2010) Treatment options for paediatric pulmonary arterial hypertension. Eur Respir Rev 19(118):321–330
9. Berger RM, Beghetti M, Humpl T, Raskob GE, Ivy DD, Jing ZC, Bonnet D, Schulze-Neick I, Barst RJ (2012) Clinical features of paediatric pulmonary hypertension: a registry study. Lancet 379(9815):537–546
10. Del Cerro MJ, Abman S, Díaz G, Freudenthal S, Freudenthal F, Harikrishnan S, Haworth SG, Ivy D, Lopes AA, Raj JU, Sandoval J, Stenmark K, Adatia I (2011) A consensus approach to the classification of pediatric pulmonary hypertensive vascular disease: report from the PVRI pediatric taskforce, Panama 2011. Pulm Circ 1(2):286–299
11. Flolan® (2012) Summary of product characteristics. GlaxoSmithKline, Durban
12. Haworth SG, Hislop AA (2009) Treatment and survival in children with pulmonary arterial hypertension: the UK pulmonary hypertension service for children 2001-2006. Heart 95(4):312–317
13. He B, Zhang F, Li X, Tang C, Lin G, Du J, Jin H (2010) Meta-analysis of randomized controlled trials on treatment of pulmonary arterial hypertension. Circ J 74(7):1458–1464
14. Hershey AD (2005) What is the impact, prevalence, disability, and quality of life of pediatric headache? Curr Pain Headache Rep 9:34–344
15. Kim HS, Conklin JL, Park H (2006) The effect of sildenafil on segmental oesophageal motility and gastro-oesophageal reflux. Aliment Pharmacol Ther 24(7):1029–1036
16. Levy M, Celermajer DS, Bourges-Petit E, Del Cerro MJ, Bajolle F, Bonnet D (2011) Add-on therapy with subcutaneous treprostinil for refractory pediatric pulmonary hypertension. J Pediatr 158(4):584–588
17. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ (1981) A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 30(2):239–245
18. Oishi P, Datar SA, Fineman JR (2011) Pediatric pulmonary arterial hypertension: current and emerging therapeutic options. Expert Opin Pharmacother 12(12):1845–1864
19. Remodulin® (2011) Label Information. United Therapeutics Corporation, New York
20. Revatio® (2010) Summary of product characteristics. Pfizer Limited, Mumbai
21. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, Elliott CG, Gladwin MT, Jing ZC, Krowka MJ, Langleben D, Nakanishi N, Souza R (2009) Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 54(1 Suppl):S43–S54
22. Thelin® (2006) Summary of product characteristics. Pfizer Limited, Mumbai
23. Tracleer® (2007) Summary of product characteristics. Actelion Registration Ltd
24. van Loon RL, Roofthooft MT, Hillege HL, ten Harkel AD, van Osch-Gevers M, Delhaas T, Kapusta L, Strengers JL, Rammeloo L, Clur SA, Mulder BJ, Berger RM (2011) Pediatric pulmonary hypertension in the Netherlands: epidemiology and characterization during the period 1991 to 2005. Circulation 124(16):1755–1764
25. Ventavis® (2008) Summary of product characteristics. Bayer Pharma AG, Leverkusen
26. Volibris® (2008) Summary of product characteristics. Glaxo Group Ltd, Middlesex