Cardiology in the Young

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Selexipag use for paediatric pulmonary hypertension: a single centre report focussed on congenital heart disease patients

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Abstract

Pulmonary hypertension is a rare and complex disease with poor prognosis. Paediatric cases are infrequent and usually associated with congenital heart disease. Management is problematical due to the limited therapy available and poor evidence of efficacy. Recently a new medication, selexipag (Uptravi^{R}), a prostacyclin receptor agonist, has been approved for the treatment of pulmonary artery hypertension in adults. We report our experience using selexipag in four paediatric patients with pulmonary hypertension associated with congenital heart disease.

Brief Report

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Pulmonary hypertension is a complex disorder with progressive and bad prognosis. Recent paediatric guidelines were published in 2019 and the definition and classification have been mildly modified.[1,2]

Management is challenging, especially in paediatrics where there is little evidence and drugs are used off label. Treatment is based on three vasodilators: phosphodiesterase five inhibitors, endothelin receptor antagonists, and prostacyclin receptor agonists. Frequently a combination is needed.[2] The main issue with the latter group is that, until recently, only intravenous or inhaled presentations were available.

In 2016 the European Medication Agency approved selexipag, an oral prostacyclin receptor agonist. Its efficacy in pulmonary arterial hypertension has been proved in adults,[3] but paediatric data is scarce. Furthermore, selexipag use under 18 years is not yet authorised, though since 2017 a couple of off-label reports have been published.[4,5]

In our centre, we started using selexipag in 2017 as compassionate treatment in severe cases of pulmonary hypertension associated to congenital heart disease (see patient characteristics in Table 1):

Case 1

A 12-year-old male with pulmonary atresia with ventricular septum defect and major aortopulmonary collateral arteries. After initial unifocalisation and Contegra conduit placement, he had a percutaneous valve placement due to pulmonary regurgitation and right ventricle disfunction. Progressively he developed pulmonary hypertension and haemoptysis episodes. Despite double treatment (sildenafil and bosentan) and catheter interventions, he remained desaturated (81%) and in poor condition (NYHA III) with nocturnal need of oxygen. His last catheterisation showed mean pulmonary arterial pressure of 41 mmHg and resistance index of 14 WU × m^2.

He was started oral selexipag (200 mcg/12 h) as impatient to monitor adverse effects. We increased the dose weekly until he reached a 1600 mcg/12 hours dose, with no major adverse effects. On follow-up we decreased to 1400 mcg due to diarrhea and flushing, now well controlled. He reports transient non painful episodes of priapism and suffered abdominal ache that improved with concomitant food intake. Serial blood tests showed no relevant disturbances. After 3 months and for the last 2 year follow-up he has experienced a subjective improvement with no complications, NYHA II-III, better 6 minutes walk test (430 m, less dyspnea) and echocardiographic parameters.

Case 2

A 6-year-old female with pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries, with partial unifocalisation in neonatal period. She developed early lobar arteries stenosis initially stented percutaneously. Since early childhood she presents desaturation and signs of pulmonary hypertension despite double treatment (sildenafil and bosentan). She was markedly symptomatic (NYHA III) with saturation 82%, intermittent oxygen therapy and slow growth. Her last catheterisation shows mean pulmonary pressure of 40 mmHg and resistance index 17.1 WU × m^2.

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Table 1. Patients characteristics

Case	Age	Gender	Background diagnosis	Weight	Baseline treatment	PVRi (WU × m^2)
1	12 years	Male	PA + VSD + MAPCAS	28 kg	Sildenafil + bosentan	14
2	6 years	Female	PA + VSD + MAPCAS	17 kg	Sildenafil + bosentan	17.1
3	17 years	Female	Down + AVSD (corrected)	45 kg	Sildenafil + bosentan	13.2
4	21 months	Male	Complex – Glenn	10.5 kg	Sildenafil + bosentan + epoprostenol	-

AVSD = atrioventricular septal defect; kg = kilograms; M = months; MAPCAS = major aortopulmonary collateral arteries; PA = pulmonary atresia; PVRi = pulmonary vacular resistance index; VSD = ventricular septal defect; Y = years.

Table 2. Effect and side effects of selexipag

Case	Treatment duration	Maximum dose (mcg)	NYHA (pre/post)	6-mwt (pre/post)	PVRi post	Benefits	Side effects
1	39 m	1400 (50/kg)	III–IV/II–III	280/430 78%/81%	6.8	Less basal dyspnea	Priapism Diarrhea (needed dose change)
2	14 m	1600 (95/kg)	III/II	300/480 75%/85%	–	More active Wean O2	Minor headaches
3	21 m	1600 (35/kg)	II–III/II	350/450 97%/97%	–	Better exercise tolerance	Flushing Jaw pain
4	12 m	1200 (115/kg)	IV/III–IV	–	–	Wean epoprostenol Discharge	Mild diarrhea

6-mwt = six-minute walk test (meters and minimal oxygen saturation); kg = kilogram; m = months; mcg = micrograms; PVRi = pulmonary vacular resistance index (measured in WU × m^2).

She was started selexipag as outpatient (initially 200 mcg/12 hours) and she is currently on 1600 mcg/12 hours. She has not experienced any major adverse effects, only minor headaches that have resolved. On follow-up she shows clear symptomatic improvement: more active, doesn't require nocturnal oxygen; though echocardiography and O2 saturation remain similar.

Case 3

A 17-year-old female with background of 21 trisomy and complete atrioventricular canal corrected by 9 months of age with no residual relevant lesions. By 4 years, she developed pulmonary hypertension that was medically treated (sildenafil and bosentan). On last visits, she was mildly affected (NYHA II-III, 97% saturation with no desaturation in 6 minutes walk test, where she performed 350 m), with moderate right disfunction on magnetic resonance imaging and high pulmonary vascular resistance index (13.2 WU ×m^2) in catheterisation.

She was started on 200 mcg selexipag/12 hours as outpatient and increased progressively until 1600 mcg/12 hours with no major side effects. She reported episodic flushing and jaw pain that receded with no intervention. For the last year, she has been stable: has an active live with mild shortness of breath with exertion, no changes in echocardiography.

Case 4

A 21-month-old male infant with a complex heart malformation: atrioventricular discordance with mirror image ventricles, double outlet right ventricle, non-commited large ventricular septal defect and transposition of the great arteries. By 4 weeks, he underwent palliative pulmonary artery banding and by 8 months a pulsed Glenn procedure. He had a complicated course with chylothorax and failure of Glenn secondary to thrombosis, with collateral circulation development. Despite serial interventions he remained in poor condition dependant of mechanical ventilation. Due to high Glenn pressures, sildenafil and bosentan were initiated. For 12 months he was stable, but presented an acute severe respiratory deterioration with expectoration of bronchial casts. In this critical context of plastic bronchitis, intravenous epoprostenol was started with good response and no further deterioration.

After a couple of weeks it was decided to transition him to oral selexipag. He was started on 200 mcg/12 hours and augmented till 800 mcg/12 hours while weaning of prostacyclin during a week. He was monitored in the intensive care unit with no relevant side effects (no change in haemodynamic or respiratory monitoring, no diarrhoea, irritability, flushing etc.). He could be discharged and has had no major complications since the start of the treatment with triple medication (sildenafil, bosentan, and selexipag 1200 mcg/12 hours).

Discussion

Pulmonary hypertension is a rare disease accounting for less than 50 cases per million children in Europe.[6] Despite the progress in treatment in the last 40 years, morbimortality remains high.

The first specific treatment developed in 1987 was prostacyclins. They had a great effect on mortality and symptoms,[7] but they could only be administered intravenously. The need of permanent central lines implied new risks and complications (infections, thrombosis etc.), limiting its use.[8] Other presentations and oral drugs are used, but prostacyclins remain the drug of choice for high risk patients with severe disease.[2]

Selexipag, an oral prostacyclin receptor agonist, has emerged as alternative to intravenous prostacyclins with promising results in adults.[3] Interest in its paediatric use has arisen since the first reports[4,5,9] and preliminary results are encouraging.

Our results are in agreement with these recent reports (see Table 2). Selexipag was well tolerated by all our patients. Mild side

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effects were seen (diarrhoea, abdominal pain, jaw pain, headaches, and priapism), all of them already reported.[3] Most were transient and appeared in the first weeks of treatment while increasing the dose. Only one of the patients required downtitration of dosage due to loose stools.

It is difficult to assess the efficacy of treatment, but in our opinion our patients experienced a benefit with selexipag: one could wean night oxygen, another could discontinue epoprostenol infusion, and the others remain stable. One has a single ventricle physiology with poor prognosis, but oral treatment has allowed him to be discharged. As far as we know, he is one of the youngest patients treated with selexipag to date (21 months). We expect to have haemodynamic invasive assessments soon supporting our results.

Concerns have been raised about dosing in paediatric patients. Selexipag is a prodrug with high bioavailability and the active drug (ACT333679) has a long half-life (6–13 hours) that allows twice per day dosing. Its metabolism and excretion is bile dependent.[10] No paediatric data exist to date, but there are currently ongoing trials investigating the right dosage in patients over 2 years (NCT03492177) (EudraCT Number: 2018-000145-39). Due to the lack of data, we titrated the dose empirically weekly as stated in other papers. There are reports of significant desaturation with high doses due to intrapulmonary right-to-left shunting that merits downtitration. We targeted maximum tolerated dose (according to adult data) and we did not experience any issue of the kind.

We acknowledge that our data is very limited and no strong conclusions can be drawn. But we consider that it's encouraging to get safety information on such a promising new drug. New trials are ongoing regarding efficacy in paediatric patients already (EudraCT number 2019-002817-21) and will guide future management.

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Conflicts of interest. None.

Ethical standards. We received approval from our local Ethics Committee to review the data retrospectively and publish our findings. We collected Informed Consent from our patients or our patients guardians to collect the clinical data and publish it. Confidentiality was assured.

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