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Sildenafil for pulmonary hypertension treatment after cardiac surgery

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Abstract

Objective: To report on the use of sildenafil for pulmonary hypertension treatment of a newborn patient after cardiac surgery.

Description: A female, full term newborn infant with diagnosis of double outlet right ventricle, pulmonary hypoplasia and subaortic ventricular septal defect, was submitted to Blalock surgery in the first week of life. In postoperative the newborn had pulmonary hypertension and persistent hypoxia, without response to nitric oxide, but with improved oxygenation after continuous intravenous infusion of prostaglandin E1. After several failed attempts to discontinue prostaglandin E1, oral sildenafil was used. There was a decrease in pulmonary vascular resistance with consequent oxygenation improvement and 48 hours later it was possible to discontinue prostaglandin E1 infusion.

Comments: Sildenafil can be an alternative therapy for pulmonary hypertension, especially when there is no response to conventional therapy.

J Pediatr (Rio J). 2005;81(2):175-8: Sildenafil, pulmonary hypertension, prostaglandin.

Introduction

Pulmonary hypertension, a disease that causes high morbidity and mortality in childhood, and has a multifactorial etiology, occurs in approximately 1.9 in every 1,000 live births. It is characterized by an increase in pulmonary vascular resistance, resulting in a right-to-left shunt with deoxygenated blood flow through the ductus arteriosus or foramen ovale.[1]

The aim of the treatment is to stabilize the cardiovascular function, improve oxygenation and reduce pulmonary arterial pressure. The treatment of pulmonary hypertension[1-3] includes oxygen, calcium channel antagonists, prostacyclin and analogues, endothelin receptor antagonists and vasodilators, such as nitric oxide. However, despite therapeutic advances, only 50% of the patients show a clinical response.[1] Thus, new treatment options have been investigated, including phosphodiesterase-5 inhibitors, such as sildenafil, which increases the concentration of cyclic guanosine monophosphate (cGMP) and causes pulmonary vasodilation.[4,5]

Case report

Full-term female newborn weighing 2,550g submitted to echocardiogram and cardiac catheterization and diagnosed with double outlet right ventricle, hypoplasia of the pulmonary trunk, and subaortic ventricular septal defect (VSD). The patient was submitted to a Blalock shunt in the first week of life. In the postoperative period,

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she presented with pulmonary hypertension (76mmHg), diagnosed by cardiac catheterization, and persistent hypoxemia without any underlying pulmonary disorder. She had a 70% oxygen saturation, did not respond to treatment, not even to conventional mechanical ventilation and inhaled nitric oxide (20 ppm). Oxygen was improved on the 18th day of life (11th postoperative day), after the initiation of continuous intravenous infusion of prostaglandin E1(PGE1). At 50 days of life, after several unsuccessful attempts to discontinue PGE1 therapy, and after her parents signed a consent form, oral administration of sildenafil was initiated in the dose of 0.5 mg/kg, given every six hours. Pulmonary arterial pressure, measured by Doppler echocardiogram 4 hours before the first dose of sildenafil, corresponded to 70 mmHg and dropped to 55 mmHg 24 hours after medication use. By the end of the first week of treatment, pulmonary pressure was 38mmHg. The effects on oxygenation were observed in the first 24 hours after medication use, with discontinuation of PGE1 infusion after 48 hours, maintaining room-air oxygen saturation around 90%. No hypotension or any other side effects were observed. Arterial pressure was monitored by noninvasive methods every hour during the first 24 hours of sildenafil administration, being later monitored on a regular basis before and after the drug administration. The patient was discharged 15 days later, and the use of sildenafil was maintained for 30 days, being gradually withdrawn, with no intercurrent events.

The behavior of ventilatory and cardiovascular parameters towards the treatments used is shown in Table 1.

Discussion

The lack of response to conventional therapy and the need to maintain continuous IV drug infusion, which is costly and not free from side effects, encouraged us to seek new treatment options. Studies and reports of the oral administration of sildenafil seemed to be promising and were a determining factor for its use.[6-9]

Sildenafil was studied in animal models of pulmonary hypertension, revealing to be a selective pulmonary vasodilator with no effects on systemic arterial pressure, enhancing the effects of inhaled nitric oxide (iNO) when given orally or intravenously.[5,10] It is a potent inhibitor of phosphodiesterase-5, which is responsible for the conversion of cGMP into GMP. The inhibition of this enzyme results in an increase of cGMP concentration in the lungs, with consequent relaxation of the smooth muscle of the vascular wall (Figure 1).[6]

This medicine is available for oral administration, is well-absorbed by the gastrointestinal tract, and starts acting 15 minutes after administration. It has a half-life of 4 hours, and it is excreted by the liver. Side effects include headache, rubor, dizziness, dyspepsia, nasal congestion and visual disorders. The dose used for pulmonary vasodilation in adults corresponds to 25-50% of the dose recommended for the treatment of erectile dysfunction. The recommended dose for children ranges from 1 to 2 mg/kg/day.[6,11]

Studies carried out in adults with pulmonary hypertension showed reduction in pulmonary vascular resistance after sildenafil monotherapy or its combination with prostacyclin[12] or iNO.[13]

Table 1 - Ventilatory and cardiovascular parameters

Parameters	Immediate PO	Nitric Oxide *	PGE1 †	PGE1 ‡ before-Sildenafil	PGE1 ‡ + Sildenafil § after 24 hours	Sildenafil §
Days of life	7	15	18	50	51	58
IfO_2	1.0	1.0	0.6	0.5	0.4	0.21
Sat O_2 (%)	60	70	95	96%	96	90
PaO_2 (mmHg)	26	37	70	81	75	60
MAP	12	12	–	–	–	–
PAM (mmHg)	48	55	80	78	75	65
PAP (mmHg)	70	76 ¦	70	70	55	38
D (A-a) O_2	591	580	286	210	151	37

PO = postoperative; IfO_2 = inspired fraction of oxygen; Sat O_2 = oxygen saturation (pulse oximetry); PaO_2 = partial oxygen pressure (arterial gasometry); MAP = mean airway pressure; PAM = mean arterial pressure (noninvasive monitoring); PAP = pulmonary artery pressure (Doppler echocardiogram); PGE1 = prostaglandin E1; D (A-a) O_2 = Alveolar-arterial oxygen difference.

* 20 ppm, inhaled.
† 0.1 µg/kg/min, endovenous.
‡ 0.05 µg/kg/min, endovenous.
§ 2 mg/kg/day, oral.
¦ cardiac catheterization.

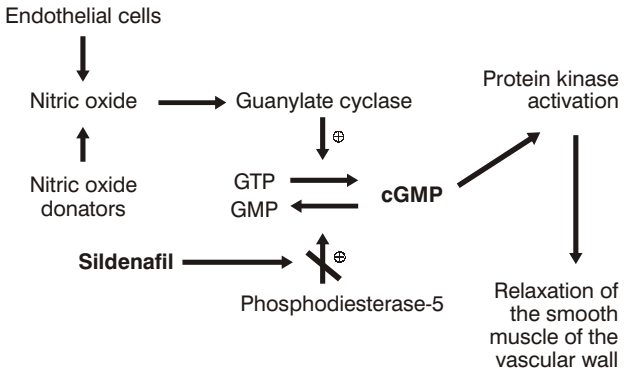

Figure 1 - Sildenafil action mechanism algorithm, modified by Abrams et al.[6]

The effects of sildenafil on pulmonary vessels do not depend on the etiology of pulmonary hypertension, which varies with age. In the neonatal period, pulmonary hypertension can occur due to meconium aspiration, sepsis, pneumonia, perinatal asphyxia, congenital diaphragmatic hernia, and pulmonary hypoplasia; in childhood, in general, it is associated with pulmonary diseases or sequelae of interstitial pneumonitis.[1] Hypertension secondary to congenital heart disease occurs independently of age.

The use of sildenafil in children has been described only in case reports[6-9] and in one randomized study that compared the use of iNO and intravenous sildenafil.[14]

There are three reports of pulmonary hypertension after heart surgery in infants aged 1 day, 6 weeks and 4 months. These infants were treated with oral sildenafil (1 mg) combined with iNO after several unsuccessful attempts to discontinue the administration of nitric oxide. After the introduction of sildenafil, there was a decrease in pulmonary arterial pressure, with no change to systemic blood pressure, and then it was possible to suspend the use of iNO. [7] A randomized study involving 15 newborns submitted to heart surgery for the correction of the ventricular and atrioventricular septal defects assessed the use of iNO and intravenous sildenafil: seven newborns initially received iNO (20ppm) and later sildenafil (0.35 mg/kg), and eight newborns received sildenafil and later iNO. Despite pulmonary vasodilation, which enhanced the effect of iNO in both groups, sildenafil reduced systemic blood pressure, leading to systemic hypotension and, consequently, worsening oxygenation, probably due to the increase in the intrapulmonary shunt. In spite of some methodological limitations, the study shows that new studies are necessary since undesirable effects that had not been described yet, such as hypotension, were observed.[14]

In case of idiopathic hypertension, there is a report of sildenafil use in a 4-year-old child who did not respond to nitric oxide therapy, but who had a decrease in pulmonary arterial pressure after prostacyclin administration. Sildenafil was indicated in the dose of 2 mg/kg/day, given orally every 6 hours, to reduce the long-term effects of prostacyclin, including bone disorders such as hyperostosis, cortical proliferation and periostitis. Prostacyclin was successfully withdrawn.[6]

Erickson et al.[8] used oral sildenafil in 24 children, of whom five were newborns, all of them with refractory pulmonary hypertension, after the gradual withdrawal of iNO. Sildenafil allowed for the discontinuation of iNO in all patients, without causing any instability to them. Recently, Carrol & Dhillon[9] have reported the use of sildenafil in three children, one case after cardiac surgery, with a good response, and two cases with pulmonary hypertension secondary to interstitial pneumonitis. One of them did not respond to treatment, probably due to the severity of the symptoms and delayed use of the drug.

In our case, nitric oxide was not efficient in treating pulmonary hypertension. Inhaled nitric oxide is the most important vasodilator with a selective pulmonary effect, improving the prognosis of hypoxemic patients and reducing mortality and the necessity of extra corporeal membrane oxygenation (ECMO). However, approximately 50% of the patients did not respond to this therapy as they presented either with severe pulmonary parenchymal diseases, myocardial dysfunction or disorders related to the nitric oxide and cGMP ratio.[11] The preexisting myocardial dysfunction in our patient may explain the lack of response to nitric oxide therapy, but interestingly enough, the patient responded to continuous PGE1 infusion.

Prostacyclins, PGE1 and I2 are important pulmonary vasodilators under hypoxic conditions, and have vasoactive effects on neonatal and fetal pulmonary circulation and a synergic effect with other drugs such as phosphodiesterase inhibitors.[2,15] Prostacyclin has a shorter half-life than PGE1, around 1 or 2 minutes, has a poorer effect on platelet activation and reduces pulmonary vasoconstriction.[15]

The good response of our patient suggests that sildenafil may play a role in the treatment of pulmonary hypertension after cardiac surgery, being considered nowadays as a rescue treatment for those patients who did not respond to conventional therapy. Oral administration is another aspect to be considered, since it avoids long-term complications arising from the use of prostaglandin/prostacyclin and allows reducing the length of hospital stay.

Due to the paucity of data in the literature, and because it is a new medication, still in the experimental phase, being used as rescue treatment of severe pulmonary hypertension in human beings, especially in newborns, we expect this case report to show that the use of sildenafil was beneficial as a pulmonary vasodilator, allowing for the discontinuation of PGE1 without causing short-term adverse effects on the patient.

Sildenafil seems to be a promising agent for the treatment of pulmonary hypertension, but several issues require further investigation before the use of this medication can be recommended. One of these issues concerns the interaction of phosphodiesterase-5 enzyme and its distribution to extrapulmonary tissues, the effects of sildenafil on the myocardial function and on pulmonary

gas exchange, the systemic hemodynamic effect on the occurrence of sepsis and the effect on patients with hepatic dysfunction.

The available data indicate the necessity for randomized clinical trials to evaluate the efficiency and safety of this drug for the treatment of pulmonary hypertension. Also, pharmacological studies are necessary in order to determine its dose and the safest route of administration in newborns and children.

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