The clinical case of sildenafil administration in a very premature infant with pulmonary hypertension

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Abstract

We report the use of oral sildenafil in a 7-month-old preterm newborn with severe bronchopulmonary dysplasia and pulmonary arterial hypertension refractory to captopril and inhaled budesonide, and need of consistent oxygenation. Sildenafil was prepared as a powder for oral administration. Oral sildenafil treatment was continued for 11 months. Oxygen supplement was suspended after 4 months and captopril administration was finished after 7 months of sildenafil treatment. There were no adverse effects during the treatment period. The respiratory failure decreased significantly and pulmonary arterial pressure became normal after 7 months of sildenafil treatment.

Keywords

Sildenafil, bronchopulmonary dysplasia, pulmonary arterial hypertension, premature infants.

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Introduction

Bronchopulmonary dysplasia (BPD) is a multifactorial chronic lung disease, mainly of premature infants, treated with long-term ventilation for acute respiratory failure. The clinical features of BPD are persistent respiratory failure, hypoxemia and an abnormal chest radiograph [1]. The incidence of BPD ranges between 6.9% to 57%, and in most cases BPD affects infants with birth weight lower than 1,000 g [1-4]. The severity of BPD decreases with the introduction of continuous airway pressure ventilation, but the mortality in infants with BPD remains 23-36% [2, 4]. Premature babies with severe BPD may develop pulmonary arterial hypertension (PAH), cor pulmonale, right ventricular hypertrophy and systemic arterial hypertension. PAH increases the mortality risk in 14-52% of patients [2, 4-7]. The development of PAH is related to abnormal lung circulation in infants with BPD (i.e. increased vascular tone, hypertensive remodeling and decreased vascular growth), reduction of small pulmonary arteries and altered distribution of pulmonary arteries within the pulmonary interstitium, which causes reduction of alveolar-capillary surface area. This reduction in surface area causes an impairment of gas exchange and increases the requirement for prolonged oxygen and ventilation treatment, which raises the risk of PAH. The detection of PAH in premature infants with BPD may be difficult because its manifesting symptoms may be subtle [4]. Electrocardiography and echocardiography may be used for the evaluation of PAH in infants with BPD. PAH is usually calculated from tricuspid insufficiency by using the modified Bernoulli’s formula (maximum gradient right ventricle/right atrium) + right atrial estimated pressure (about 10 mmHg if right atrium is enlarged). The estimation of pulmonary artery pressure (particularly, the gradient right ventricle/ right atrium) may not be possible in young children. In these cases other echocardiography findings (such as right atrial enlargement, right ventricular dilation or hypertrophy, septal flattening, increased velocity of pulmonary valve regurgitation, etc.) might be suggestive of PAH [4-5].

All the children with BPD and PAH require an adequate treatment. The consistent oxygenation is essential, because the chronic hypoxia induces pulmonary vascular constriction that promotes the aggravation of PAH [4, 10]. Some patients require the administration of selective pulmonary vasodilators to decrease pulmonary arterial pressure. The efficiency of inhaled nitric oxide (NO) and inhaled prostacyclin was described in many studies [2, 4, 8-11].

According to recommendations of treatment of PAH [5], sildenafil can be used in infants with severe BPD and PAH. Sildenafil is a highly selective phosphodiesterase type-5 inhibitor, which increases cyclic GMP in the pulmonary vascular smooth muscle cells and decreases pulmonary vascular resistance. There are no standards of sildenafil administration in premature infants with BPD and PAH; the initial dose of 0.25-0.5 mg/kg 3-4 times a day was reported; the top dose without systemic hypotension effect is 8 mg/kg/day [2, 4, 7, 11-13].

We present a clinical case of beneficial effect of sildenafil in premature boy with severe BPD and PAH.

Case report

We report a case of severe BPD in preterm newborn (male, gestational age 31-32 weeks, birth weight 1,250 g, birth height 42 cm). The boy was born by emergency cesarean section because of preterm discharge of amniotic fluid. He had a severe respiratory failure and needed an intubation and intermittent positive pressure ventilation for 32 days. The surfactant was administered at 5 minutes of life and in 7 more occasions in the first 2 weeks of life because of the severity of respiratory failure. From the 33rd day of life the boy was consistently oxygenated via nasal cannula with 30% oxygen, 2 L/min. At 5 months of life he was still in poor condition, so he was transported to hospital in Moscow. At the examination the SaO2 decreased from 94% to 70% without oxygenation and diffuse cyanosis appeared. The dyspnea at rest was 68 breaths per minute; at auscultation the crepitations and rhonchi were audible over all lung fields. The heart rate was 144-170 beats per minute. The blood pressure tended to increase to 115/75 mmHg from time to time. The patient was prescribed digoxin 0.028 mg/day (because of episodes of tachycardia to 180-200 beats per minute), captopril 0.2 mg/kg/day; inhalations with budesonide 500 μg/day and potassium-sparing diuretic 2 mg/kg/day, in accordance to standard of severe BPD treatment approved in Russian Federation. He was partially fed through feeding tube because of poor appetite and growth failure. There was no severe neurological impairment, but the child had decreased emotional response and his motor activity was reduced. The psychomotor development (CAT/CLAMS scale)
was correspondent to 2 months of age, probably because of poor somatic condition and apparent immaturity. The blood test results showed signs of moderate anemia and metabolic alkalosis. The level of thyrotrophic hormone TSH was 7.84 MU/ml, so L-thyroxin 6.25 μg/day was started. The level of free carnitine was significantly increased, which was considered as a secondary carnitine deficiency in premature baby [14], so L-carnitine 50 mg/kg/day was administered.

Because of severity of respiratory failure, the congenital malformation of lung was supposed. The CT-findings showed lung pattern deformation, pneumofibrosis, lobular atelectasis and pulmonary bullas in basal segments on both sides. At 5 months of life the cardiac ultrasound detected an open foramen ovale. There was no right ventricle dilation, and systolic pulmonary arterial pressure was normal. The captopril dose was increased to 1 mg/kg/day and furosemide 5 mg/day was started in place of potassium-sparing diuretic. After 1 week of treatment the condition of our patient improved, the dyspnea at rest decreased to 48-54 breaths per minute, the heart rate decreased to 138 beats per minute. The number of crepitations and rhonchi decreased too, as well as the level of alkalosis. The boy could stay without an additional oxygenation for 1-2 hours a day, and SaO₂ was 91-96%. There was a progress in psychomotor and physical development. Palivizumab was administered twice because of high risk of respiratory syncytial viral infection in premature infant with severe BPD.

At 6 months of life the boy’s health had worsened because of catarrhal rhinitis and obstructive bronchitis. The dyspnea and cyanosis continued, the heart rate was 148-150 beats per minute. The O₂ saturation was low (81-86%), and the boy couldn’t remain without supplementary nasal cannula oxygenation at any time. The crepitations continued, and there was no weight gain from 6 to 7 months, in spite of symptomatic therapy and nourishing diet. The echocardiographic examination at 7 months of life showed a right atrial enlargement, right ventricular dilatation, interventricular septum bulging towards the left ventricle. Estimated systolic pulmonary arterial pressure was 54 mmHg (Fig. 1).

Oral sildenafil was started in dose of 1 mg/kg once a day (6.25 mg/day) as an experimental treatment after parental consent. The hospital pharmacy prepared the oral suspension of sildenafil (Viagra®, Pfizer, New York, USA, the single drug form, registered in Russian Federation) by crushing 25-mg tablets into powder. It was then mixed with dextrose and separated into small plastic bags. Each bag contained the described dose of sildenafil (6.25 mg). The powder was dissolved in 2 ml of sterile water and administered through the orogastric tube.

**Results**

After 7 days of treatment there was a significant improvement of boy’s condition: the dyspnea decreased to 42-46 breaths per minute, the heart rate decreased to 128-134 beats per minute, the oxygen saturation was consistently over 91%. Within the first 2 weeks of sildenafil treatment the tube feeding was stopped.
Repeated echocardiogram at 14 days of treatment showed a substantial reduction in PAH as evidenced in right atrial contraction and absence of bulging septum towards the left ventricle. Estimated systolic pulmonary arterial pressure was 38 mmHg (Fig. 2). The boy was discharged from hospital at 9 months of life, and control echocardiograms were recommended once a month. Digoxin, furosemide and L-thyroxin were gradually suspended at 9 months, and captopril – at 14 months. The boy was gradually weaned off oxygen at 11 months.

On planned follow-up at 14 months of life, the boy was in a stable condition. The weight was 7,900 g, the height was 75 cm. There were no adventitious breath sounds on chest auscultation; a moderate exertional pant was noted. Estimated systolic pulmonary arterial pressure was 21 mmHg. The boy had significant catch-up in motor development, and moderate cognitive and speech developmental delay. The dose of sildenafil was decreased to 4 mg/day. The boy was gradually weaned off sildenafil at 18 months.

**Discussion**

PAH aggravates respiratory failure in premature infants with severe BPD. Decreased oxygen saturation creates conditions for chronic hypoxia, which can have a negative effect on brain development. Our patient demonstrated a rapid improvement in PAH as evidenced by an increase in the oxygen saturation and disappearance of echocardiac abnormalities after 7 days of sildenafil use. We also did not see the respiratory failure after 5 months of treatment. Sildenafil had lasting beneficial effect, however, the course of treatment was very long. No adverse effects were observed on systemic blood pressure or flushing during the treatment period, in spite of digoxin and captopril weaning. At 18 months we observed essential cognitive development delay in our patient. It can either be due to apparent immaturity, or the result of prolonged hypoxia. Initially, at 5 months of life, we have not seen the echocardiographic signs of PAH, but transthoracic echocardiographic examination may present some difficulties in a little children. Perhaps, the sildenafil administration should have been started earlier.

The optimal dose for infants has not been determined, so we adopted the dosage described by Buck [11] in review of sildenafil treatment in children with PAH.

In conclusion, this case report illustrates the beneficial effect of oral sildenafil in infant with severe BPD and secondary PAH. Sildenafil should be considered for administration in case of lack of effectiveness of standard therapy.

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**Declaration of interest**

The Authors declare that there is no conflict of interest.

**References**


