Effects of long-term oral sildenafil treatment for pulmonary hypertension in infant with bronchopulmonary dysplasia. Physical and psychological implication in a case report

F. De Luca\textsuperscript{1}, V. Leanza\textsuperscript{2}, G. Leanza\textsuperscript{2}, A. Privitera\textsuperscript{1}, N.H. Silverman\textsuperscript{3}

**Summary:** Effects of long-term oral sildenafil treatment for pulmonary hypertension in infant with bronchopulmonary dysplasia. Physical and psychological implication in a case report.

F. De Luca, V. Leanza, G. Leanza, A. Privitera, N.H. Silverman

Introduction. The indication to use sildenafil is still off label in many countries and no results from controlled clinical trials, nor shared guidelines are available. Its clinical maybe advantageous especially in those areas where medical aids and medications such as high frequency ventilation, nitric oxide and surfactant are not available for infants with pulmonary hypertension.

Case presentation. A preterm infant with severe pulmonary hypertension, associated with bronchopulmonary dysplasia, was treated with oral sildenafil in combination with nitric oxide.

Conclusions. Beside an evident clinical improvement, sildenafil has led to a significant reduction of pulmonary hypertension. Thus we proved that a long-term oral sildenafil therapy as part of an aggressive treatment program is well-tolerated without significant adverse events.

Key words: High pulmonary blood pressure - Vasodilators - Treatment - Preterm newborn - Psychological implications.

Introduction

Pulmonary hypertension (PH) is a severe complication which affects infants with bronchopulmonary dysplasia (BPD) and contributes to increase the long-term mortality rate (52% within 2 years after diagnosis). The role and efficacy of the long-term therapy with nitric oxide and/or calcium agonists have not been clearly defined yet. On the basis of the results reached so far, the adoption of a more aggressive therapeutic program may be rational. The use of sildenafil, as single agent or in combination with other therapies, has been proposed as a possible therapeutic option for these subjects with pulmonary hypertension and chronic pulmonary disease, as widely documented with randomized trials in adult patients with PH (1-3). Sildenafil, as selective phosphodiesterase type-5 inhibitor decreases pulmonary vaso-
lar resistance, causing a selective vasodilatation by increasing cyclic guanosine monophosphate (cGMP). Many reports have demonstrated that the oral use of sildenafil in term or preterm infants, suffering from primitive or secondary pulmonary hypertension (PH) and severe hypoxemia, improves the survival rate without causing significant adverse events (4, 5). In many parts of the world these observations have caused a widespread use of this treatment for PH, even though the indication is still off label in many countries and no results from controlled clinical trials and shared guidelines are available. We thought that its clinical use can prove to be particularly useful, especially in those areas where medical aids and medications such as high frequency ventilation, nitric oxide and surfactant are not available for infants with PH.

Case presentation

S.R. was a small for gestational age (SGA) infant, born in April 2007 by emergency caesarean section (CS), performed at the 29th week, due to the onset of severe pre-eclampsia in week 28. The mother had a placental insufficiency accompanied by oligohydramnios identified at 20 weeks. The newborn was fed with parenteral nutrition from the first day and started therapy with nitric oxide (NO), diuretics and positive inotropes (digoxin). Birth weight was 560 g, height 30 cm, cranial circumference 22 cm and Apgar score 3/6. Chest X-ray showed hyperlucency of the basal retrocardiac region, increased pulmonary air content, accentuation of the interstitial lines. Chest CT scan showed wide areas of parenchymal consolidation, atelectatic regions, widespread signs of interstitial emphysema, accentuation of the vascular markings and widespread signs of stasis.

During the first months of life, the infant needed permanent oxygen therapy administered by nasal cannulation. At five months of life, weight was 2.620 g, height 50 cm and cranial circumference 33.5 cm. A jejunostomy was carried out to facilitate continuous enteral feeding. A new chest X-ray showed a further enlargement of the regions characterized by pulmonary parenchymal hyperlucency, with persisting parenchymal hyperexpansion and a marked cardiomegaly (CI 0.68). Serial echocardiography showed considerable dilatation of right ventricle (Figure 1) and pulmonary artery trunk, with flattening of ventricular septum. A tricuspid and pulmonary regurgitation (Figure 2) was recorded using continuous-wave Doppler. At 5 months, a cardiac catheterization showed the dilation of all right sections and pulmonary artery trunk, as well as supra-systemic pulmonary hypertension. At 155 days, it was decided to start oral sildenafil therapy at the dose of 0.4 mg/kg gradually increasing up to 1 mg/kg every 4-6 hours, when the desired clinical re-
sult was reached. After 90 days of therapy, echocardiography showed a significant improvement of hemodynamic conditions: at least a 20% reduction of pulmonary systolic pressure/systemic systolic pressure ratio and a reduced flattening of the ventricular septum kinetics, without evident adverse events. Therefore, the therapy with digoxin was discontinued, diuretic therapy (spironolactone and hydrochlorothiazide) was reduced, oxygen therapy was turned from permanent into night therapy only, without evident decrease of the O2 saturation levels, monitored to ensure they remained within a 92-96% range. Sildenafil dosing regimen was then gradually reduced over a period of 4 weeks, until its discontinuation after 900 days since its start. From a psychological point of view, as a result of the difficult medical framework, the patient showed both an impaired response to stress and an altered attachment behaviour, which is relevant, as the exposure to abuse, for the development of psychological disorders (6, 7).

Discussion and conclusions

The case of an infant suffering from BPD and PH treated with sildenafil is here described where long-term oral sildenafil therapy, as part of an aggressive treatment program to treat infant suffering from BPD and PH, was well-tolerated, related to progressive improvement in PH, without significant adverse events (Figure 2).

Our results are encouraging and suggest that randomized clinical trials are needed with the objective of better defining the optimal dosing regimen (dose and duration), as well as the efficacy and clinical safety of sildenafil. This therapeutic approach seems very promising as it can prove to be particularly useful in those areas with limited resources, where medical aids and medications such as high frequency ventilation, nitric oxide and surfactant are not available for infants with PH. Thus, we proved that sometime an aggressive treatment program leads to clinical improvements.
without significant adverse events (8-12). However, despite the medical efficacy of treatment, when severe health problems occur, psychological support is imperative for both infants and mothers’ physical and psychological well-being. Thus it is important to identify the women who may benefit from focused perinatal psychotherapeutic treatment. Sometimes women feel ashamed or uncomfortable about seeking health care (13, 14): the modified concept (15-19) of “woman that needs help” is considered in a different way from the simple concept “woman”, causing a sort of stigmatization of the person who seeks support. Thus a good relationship doctor-patient is crucial before and after delivery, in particular when complications occur (20-28).

References