Use of Sildenafil in Pulmonary Hypertension Associated with Bronchopulmonary Dysplasia in premature infants. Single Center Experience.

A.M. Colli1, 3, M. Pierro2, E. Ciaramoli2, MA Galli1, S. Gangi1, V. Cecchini1, P. Salicce1, F. Schena2, M.R. Colnaghi2, F. Maglioli Carpano2, F. Magrini1,2, F. Mosca1,2,3

1) Paediatric Cardiology, BECCS Fondazione Ospedale Maggiore “Ca’ Granda” Policlinico, Milan, Italy
2) Neonatal Intensive Care Unit, BECCS Fondazione Ospedale Maggiore “Ca’ Granda” Policlinico, Milan, Italy
3) Università degli Studi di Milano, Milan, Italy

BACKGROUND

Pulmonary Hypertension (PH) is an emerging potentially lethal cardiovascular complication of bronchopulmonary dysplasia (BPD) [defined as O2 need at 36 weeks Post Menstrual Age (PMA)] in premature infants. Reduction of cross-sectional perfusion area and abnormal muscularization of peripheral pulmonary vessels play a significant role in the pathogenesis of PH in BPD, and abnormal vascular development conversely may contribute to the development of BPD.

The true prevalence of PH in BPD and the morbidity and mortality attributable to PH in this group are largely unknown. PH in this population must be actively looked for as symptoms may be subtle. Nitric oxide (NO) and sildenafil citrate (S) (a highly selective PDE-5 inhibitor) have been used in managing acute PH in preterm and term newborns. Sildenafil has been used successfully in older patienten with PH but only few and predominantly anecdotal reports are available on treatment of PH in newborns with BPD and one randomized study failed to show an effect of sildenafil on the development of BPD. At present no long term treatment of PH in BPD is as yet standardized. In our unit we elected to treat BPD related PH with sildenafil up to normalization of pulmonary arterial pressure (PAP) or discontinuation because of adverse effects.

AIM OF THE STUDY

To evaluate sildenafil safety and results of use in BPD related PH in a homogeneous population from a single Unit.

MATERIALS AND METHODS

VLBW infants born between 2007 and 2011 who developed BPD with concomitant PH were identified. PH is defined as systolic pulmonary artery pressure (sPAP) determined by CW Doppler evaluation of the TR jet+ estimated RA pressure >40 mmHg. Additional information was sought by septal position and eccentricity index of LV short axis. Sildenafil was started during hospital stay and continued as chronic treatment whenever PH was present and infants were on diuretic treatment (hydrochlorothiazide and spironolactone) as well as O2 supplementation.

Sildenafil was administered as oral preparation at the dose of 2-4 mg/kg/day in 3-4 daily doses and it was discontinued when PAP was normal at 2 subsequent evaluations and no additional signs of RV deformity were present. Cardiac evaluation by clinical examination and 2D echocardiogram and Doppler were performed at least weekly during hospitalization and monthly or as often as required during follow up. Safety was assessed by adverse events during treatment and need to discontinue sildenafil for reasons other than clinical improvement and normalization of PAP. Data were analyzed with SPSSv 18. Continuous variables are expressed as mean ± SD and dichotomic variables as number (percentage).

RESULTS

Between 01/ 2007 and 12/2011, 649 VLBW infants were admitted in our unit. Mean GA (PMA) and birth weight were 29±2.8 weeks and 1136±274 grams respectively. 45 patients died before 36 weeks PMA leaving 604 patients for analysis. 87/604 (14.2%) developed BPD, severe in 51 (8.4%, 58.6 of BPD patients).

PH was detected in 14/87 (16%), all with severe BPD, and they were treated with sildenafil (2.5±1.25 mg/kg/day).

The incidence of PH in severe BPD was therefore 27% (14/51). Mean PMA at diagnosis was 46±9.7 weeks and mean PAP 53±16 mmHg. Of the 14 PH patients 3 (21%) died before discharge of complications of prematurity, chronic respiratory failure and PH despite treatment, 3 (21%) achieved a normal PAP during hospitalization and discontinued sildenafil before discharge. The normal PH is maintained during 11, 9 and 8 months follow up respectively. 8/14 patients (57%) were discharged on sildenafil because of persistent PH and were followed monthly. Sildenafil was successfully weaned by 5.2±4.7 months corrected age in 5/14 patients (33.8%). 3 patients are still under treatment at 18, 22 and 39 months corrected age. 64% of PH patients (8/14) achieved normal PAP with treatment and discontinued O2 and diuretics.

There were no adverse effects related to chronic sildenafil treatment in our small series and treatment was discontinued only because of normalization of PAP. The 3 deaths were unrelated to sildenafil treatment.

CONCLUSIONS

PH is emerging as a serious and increasingly common problem in premature infants with BPD and appears to occur in those in whom BPD is most severe. Despite significant mortality from complications of BPD in this group, PH has shown to regress in more than half of the patients with medium-term treatment without significant side effects.

Larger series (possibly from cooperative studies) will be necessary to firmly establish the role of chronic sildenafil use in BPD related PH.

References