Use of Sildenafil in the treatment of pulmonary hypertension. Experience of Sudan Heart Centre.

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Abstract:

Sildenafil is a selective pulmonary vasodilator that had been introduced recently for the treatment of pulmonary hypertension. We used Sildenafil (Viagra, Pfizer) in 11 patients with pulmonary hypertension divided into 2 groups. Group 1 were 4 patients without cardiac disease: 3 with primary pulmonary hypertension and one with possible connective tissue disease. Group 2 were 7 patients who had cardiac surgery (6 for congenital heart disease and one for mitral valve replacement).

Results: In all patients there was a significant improvement in clinical and echocardiographic parameters of pulmonary hypertension. The effect was more pronounced in group 2 who were all weaned successfully from Sildenafil without side effects. One patient in Group 1 experienced periods of incoherent speech 18 months after the use of Sildenafil.

Conclusion: Sildenafil is an effective and safe drug for the treatment of pulmonary hypertension especially in post-operative patients.

Introduction:

Pulmonary arterial hypertension (PHT) is a disease of the small pulmonary arteries that is characterized by vascular proliferation

and remodeling due to different pathological and aetiological factors leading to elevation of the pulmonary artery pressure (1). Once it has been established it carries a progressive course with a poor outcome and currently has no cure. In the last 20 years many drugs had been evaluated for the control of symptoms including calcium channel blockers, nitric oxide and prostacyclins with variable success (2). Recently endothelin receptor antagonist (Bosentan) and phosphodiesterase 5 inhibitor (Sildenafil) had been introduced as effective and selective pulmonary vasodilators. Sildenafil acts by enhancing nitric oxide–dependent, cGMP-mediated pulmonary vasodilatation through inhibition of the breakdown of cGMP by phosphodiesterase type 5. The experience with Bosentan in children is still small (3) while that with Sildenafil had been consolidated by many large scale adult studies as well as many paediatric reports. (4,5,6,7). We report our experience with Sildenafil in the treatment of PHT in Sudan Heart Centre.

Patients and Methods

The study is a retrospective review of all patients seen at the Sudan Heart Centre (SHC) in the Paediatric Cardiology section from July 2004 to May 2006. Patients were evaluated clinically, by chest X-Ray and electrocardiogram. Complete 2 dimensional echocardiogram with Doppler was done for each patient at the first visit and at 3-4 month follow up.

Diagnosis of Pulmonary Hypertension:

Diagnosis was based on clinical examination and echocardiographic evidence with or without electrocardiographic support. Cardiac catheterization is considered the gold standard for diagnosis and was performed in selected patients. Primary PHT

is defined as PHT in the absence of primary cardiac, lung or other disease known to be associated with PHT.

1. Clinical features: Signs of right heart failure: increased jugular venous pressure, hepatomegaly and lower limb oedema in older children. In infants episodic cyanosis and respiratory distress. Low oxygen saturation below 92% with clubbing in long standing cases.
2. Echocardiogrphic features which are: dilated right atrium and ventricle, tricuspid regurgitation gradient measured on continuous wave Doppler above 50% of the systemic blood pressure with or without right to left shunt across heart defects like patent foramen ovale, atrial septal defect (ASD) or ventricular septal defect (VSD) if present
3. Electrocardiographic features: right ventricle hypertrophy , right atrial enlargement with or without right axis deviation.
4. Cardiac Catheterization: Finding of pulmonary artery mean pressure more than 25 mmHg and the presence of systemic desaturation.

Other Investigations:

1. Chest X ray to evaluate lung pathology
2. Screening for connective tissue disease by doing anti nuclear antibodies
3. Screening for coagulation disorders.
4. Chest CT scan to further evaluate the lungs if there is doubt of chronic lung disease.

Management of Pulmonary Hypertension:

We started all symptomatic patients on furosemide 1-2 mg/kg/day. Spironolactone is added when we reach the dose of 2mg/kg/day of furosemide. Digoxin is used only in patients with atrial fibrillation or significant tachycardia. Sildenafil (Viagra,Pfizer) was used in the dose of 0.3 mg/kg/day and increased gradually up to 2 mg/kg/day or a dose of 25 mg BD. Follow up is arranged weekly for 2-3 weeks then 4-6 weekly.

Results:

Eleven patients with PHT were evaluated in this period. The age ranged from 10 month to 50 years, 9 patients were children and 2 were adults with congenital heart disease. Seven had PHT associated with heart disease (Group1): in 6 out of 7 this was congenital heart disease and in one it was rheumatic mitral stenosis. All 7 patients had surgery and developed symptoms in the post operative period. Four patients had PHT without cardiac disease (Group2); 3 patients had primary PHT and in one patient PHT was likely to be related to connective tissue disease. Females constituted 63% of the whole cohort and 75% of group2.

None of the patients had Down's syndrome. Patients' characteristics are shown in Table 1 (Patients with PHT without cardiac disease) and Table 2 (Patients with PHT and cardiac disease).

Patients with PHT without cardiac disease (Group 1):

All patients had signs of right heart failure. New York Heart Association (NYHA) Class was III-IV. Patient 2 had atrial fibrillation with a ventricular rate of 120 per minute. This patient had positive antinuclear antibody but all other screening tests for connective tissue disease were negative including rheumatoid factor, renal profile, eye examination and antiphospholipid antibodies. She was started on Digoxin and warfarin in addition to diuretics and Sildenafil. Consultation with rheumatologist was done and no further treatment options were suggested. Cardiac catheterization was done for 2 patients in this group (patient 3 and 4) prior to the start of Sildenafil: Patient 3 had catheterization in our centre and revealed pulmonary artery pressure of 100/60 with a mean of 70 mmHg with aortic systolic pressure of 83 mmHg, right atrial pressure mean was 30 mmHg. Patient 4 had catheterization in another centre and had pulmonary artery pressure of 95/65 with a mean of 70 and aortic systolic pressure of 90 mmHg. One patient had spiral CT of the chest which did

not reveal parynchymal lung pathology. All patients reported significant improvement in their symptoms and exercise tolerance with Sildenafil.

Patient 1 reported the occurrence of incoherent speech 18 months after starting Sildenafil while on a dose of 12.5 mg TDS. There were no other abnormal neurological symptoms or signs. The dose was reduced to 6.25 mg TDS with some improvement. No other side effects were reported.

Patients with PHT and cardiac disease (Group 2):

PHT developed in the post-operative period in all patients. Patients 1 and 3 needed long intensive care admission (7 and 10 days respectively) because of PHT and patient 2 needed re admission because of episodic cyanosis. Patient 3 was extremely sick and was ventilated with high settings and complete paralysis for 5 days during which Sildenafil was given by a nasogastric tube. In all patients echocardiogram revealed features of PHT and follow up with tricuspid regurgitation gradient revealed steady improvement consistent with improving clinical parameters. Patient 3 continued to have signs of PHT for 3 months. Trial to withdraw Sildenafil 2 months after starting resulted in deterioration of PHT clinically (cyanosis) and on echocardiogram so it was resumed and later weaned gradually without recurrence of PHT. Both patient 1 and 3 had mild to moderate left atrioventricular valve regurgitation post-operatively that continued the same during follow up. Patients 6 and 7 had VSD closure with a significant residual right to left shunt

Cardiac catheterization was done for those 2 patients (patients 6 and 7) prior to surgery. Data are available only for patient 7 which revealed a pulmonary artery pressure of 120/40 with a mean of 75 mmHg and aortic systolic pressure of 130 mmHg. All patients in this group reported an appreciable improvement in their symptoms with the use of Sildenafil but there was no

significant echocardiographic improvement. No side effects were reported.

Discussion:

Treatment options for PHT in a developing country like Sudan are limited. Drugs like nitric oxide, prostacyclins and Bosentan are not available and the latter two are extremely expensive. Sildenafil, therefore represents a specially useful drug because of its availability in the market for treatment of erectile dysfunction and its affordable price. The reports in the literature about the use of Sildenafil in children with PHT are relatively recent and the first, to our knowledge, was in the year 2000 (8). The largest reported series is by Humpl et al which included 14 patients (7). Our report includes a relatively large number of patients when we consider that paediatric cardiology specialty service started in Sudan only 6 years ago. To our knowledge, this is the first report about the use of Sildenafil in our country.

The most striking effect of Sildenafil was observed in post operative patients who had congenital and valve surgery for conditions predisposing to PHT (group1). Many of these patients were sick and needed hospitalization and re admission. Without Sildenafil this type of patients would have a high morbidity and the drug was very effective as judged by clinical and echocardiographic improvement within few days to few weeks. While post-operative patients on other therapies like nitric oxide can be difficult to wean we managed to wean all patients from Sildenafil successfully.

Moreover, the drug could help to wean patients from inhaled nitric oxide therapy as had been reported (9).

The use of Sildenafil for patients with primary PHT was associated with an appreciable sense of improvement of heart failure and some patients would express that by the phrase ' I

cannot do without the tablet'. As expected in this group we were not able to wean patients from Sildenafil as the nature of their disease is progressive. As had been reported in the literature, the drug was well tolerated with no significant side effects (6,7), however, an interesting observation was mentioned by patient no.1 in Group 2 who had a period of incoherent speech following the use of Sildenafil without any other neurological symptoms like confusion or loss of consciousness. To our knowledge, there had been no similar observation reported in the literature.

A major limitation to the objective hemodynamic assessment of the effect of Sildenafil was the high cost of cardiac catheterization which was done only for 2 patients with primary PHT and 2 with heart disease prior to the start of treatment and not done for any patient after starting Sildenafil. This difficulty of hemodynamic assessment during follow up however is not unique to our country as it is generally not practical to go for invasive studies in children if there is clear clinical improvement. A useful non- invasive assessment tool is the 6 minute walking test that could have been done for older patients.

In conclusion we presented our early results with the use of Sildenafil to treat PHT in Sudan which we think are encouraging especially for patients with post-operative PHT related to cardiac disease.

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Table 1
Patients with PHT without Cardiac Disease (Group 1):

No	age	sex	Clinical Features	Dose	Response and outcome
1	10 years	Female	NYHA class IV. Severe right heart failure	0.3 mg/kg/day increased to 2 mg/kg/day	Significant subjective improvement of exercise tolerance and tricuspid regurgitation gradient
2	15	Female	NYHA class IV. Severe right heart failure. Atrial fibrillation ANA positive. Other screening for SLE is negative	0.3 mg/kg/day increased to 2 mg/kg/day	Some subjective improvement of exercise tolerance.
3	10	Female	NYHA class III	0.3 mg/kg/day increased to 2 mg/kg/day	Lost to follow up
4	7 years	male	NYHA class IV	0.3 mg/kg/day increased to 2 mg/kg/day	Some subjective improvement of exercise tolerance

Table 2
Patients with Pulmonary Hypertension and Cardiac Disease (Group 2):

No	Age	sex	Diagnosis and clinical features	Dose	Response and outcome
1	10 months	female	Post AVSD repair with PHT in the early post operative period Needed ventilation	0.3 mg/kg/day increased to 2 mg/kg/day	PHT improved clinically and on echo over 12 weeks. Sildenfil discontinued.
2	12 months	male	Post VSD closure with PHT in the early post operative period. Needed re admission for oxygen therapy	0.3 mg/kg/day increased to 2 mg/kg/day	PHT improved clinically and on echo over 6 weeks. Sildenfil discontinued .
3	18 months	Female	Post AVSD repair with PHT in the early post operative period. Needed ventilation with sedation and muscle relaxants for 5 days.Complete atrioventricular block on pacing.	0.3 mg/kg/day increased to 2 mg/kg/day	PHT improved clinically and on echo over 12 weeks. Sildenfil discontinued .
4	14 months	male	Post superior vena cava to pulmonary artery connection (Glenn shunt) with PHT in the early post	0.3 mg/kg/day	PHT improved clinically and on echo over 1week. Sildenafil discontinued

			operative period.		
5	15 years	Female	Rheumatic mitral stenosis post mitral valve replacement. Severe biventricular failure and pulmonary hypertension in the immediate post operative period.	0.3 mg/kg/day increased to 2 mg/kg/day	PHT improved clinically and on echo over 6weeks. Sildenafil discontinued
6	22 years	Female	Eisenmenger's syndrome secondary to large VSD post surgical repair at the age of 20 years with moderate size residual VSD. NYHA class IV	12.5 mg BD	Subjective improvement of symptoms and exercise tolerance.
7	50 years	Male	Eisenmenger's syndrome secondary to large VSD closed partially at the age of 45 years. NYHA class IV	12.5 mg BD	Subjective improvement of symptoms and exercise tolerance.

Abbreviations:

AVSD: Atrio-ventriclar septal defect (AV-canal/ endocardial cushion defects)

VSD: Ventricular septal defect
PHT: Pulmonary hypertension
NYHA: New York Heart Association Classification