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Brief Report

Sudden death during a change in treatment for pulmonary hypertension

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Abstract We describe an infant with an atrioventricular septal defect and separate valvar orifices for the right and left ventricles, the so-called primum defect, who presented with serious pulmonary hypertension. Treatment with sildenafil was changed to intravenous epoprostenol due to lack of any measurable effects of the initial therapy as shown by echocardiography. The girl died three days after the change in treatment. We suggest that a mismatch between ventilation and perfusion contributed significantly to her death.

Keywords: Child; congenital cardiac disease; epoprostenol; sildenafil

Clinical experience with epoprostenol[1,2] has brought new hope for patients with pulmonary hypertension of various aetiologies. New drugs, however, tend to come to use in paediatric cardiology before any potential side-effects or complications have been fully documented. In this respect, the potential hazards of using pulmonary vasodilators to treat children with congenital cardiac disease are not fully known. We report here a detrimental experience with epoprostenol given intravenously.

Case report

The parents have given consent to us publishing this case report. In 2002, a girl with an atrioventricular septal defect, the common atrioventricular junction guarded by separate valvar orifices for the right and left ventricles, in other words the so-called primum defect, was admitted to a tertiary centre at eight months of age with pulmonary hypertension. Poor feeding and lack of gain of weight, along with excessive sweating and reduced levels of activity, had developed over the previous four months, along with episodes of near syncope. Physical findings included tachypnea, slight hepatic enlargement, and an accentuated second heart sound. Her saturation of oxygen measured transcutaneously was between 92 and 95 percent, and the blood pressure was 83/60 millimetres of mercury. Echocardiography confirmed the presence of the atrioventricular septal defect with common atrioventricular junction, shunting being left to right shunt at atrial level, with dominance of the right side of the heart. Invasive measurement of pressures in the pulmonary arteries revealed values at systemic levels. Cardiac catheterization also revealed a low saturation of oxygen in mixed venous blood of 55 percent, a slightly elevated right atrial mean pressure of 7 millimetres of mercury and a moderate shunt at the atrial level. Delivery of nitric oxide produced a decline in the mean pulmonary arterial pressure of 25 percent (Table 1).

The levels of her pulmonary hypertension were considered to represent a high risk, and the benefit of surgery was questioned. Oral sildenafil was given in an effort to reduce the pulmonary vascular resistance and achieve operability or at least reduce the risk of surgery. The dose of the drug was increased to levels of 3 milligrams per kilogram given four times daily over a period of 6 weeks. Her levels of activity increased, and the spells of crying disappeared, but no favourable effect was registered at echocardiography. Because of this, treatment was changed to continuous intravenous infusion of epoprostenol, stopping the sildenafil, and increasing the does of epoprostenol from 2.5 to 8 nanograms per kilogram per minute over two days. No side effects were registered. She showed

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Table 1. Catheterization data, pressures in millimetres of mercury.

	PT mean	FA mean	Qp/Qs	Rp/Rs
Before angio	45	48	2.0	0.43
Baseline	54	56		
After 25 minutes nitric oxide	32	46	2.5	0.22

Abbreviations: PT: pulmonary trunk; FA: femoral artery; Qp/Qs: ratio between pulmonary and systemic flows of blood; Rp/Rs: ratio between pulmonary and systemic vascular resistances

respiratory symptoms with increased tachypnoea, and wheezing ascribed to the preceding anaesthesia. Her peripheral circulation was slightly reduced. Resting saturations of oxygen were measured at levels between 91 and 96 percent, with 0.5 litres of oxygen per minute supplied through a cup. Chest radiography demonstrated no pulmonary pathology, and the size of the liver was unchanged. Blood tests showed normal findings with respect to electrolytes, C-reactive protein, haematology and capillary blood gases. Inhalations with racemic epinephrine reduced the wheezing, but were stopped because they precipitated intense attacks of crying. For similar reasons, echocardiography was considered to be of little value. On the third day of treatment, she had an episode of bradycardia that resolved spontaneously. She continued breast-feeding, receiving satisfactory amounts of milk. On the fourth day, her general condition was perceived as improving, but she still desaturated during crying and stress, accompanied on one occasion by slight bradycardia. She died suddenly after a small meal, having a picture of hypoventilation followed by bradycardia and cardiac arrest. Resuscitation was unsuccessful. Autopsy confirmed the echocardiographic findings with regard to the cardiac lesion, the atrioventricular septal defect having a diameter of 16 millimetres. The lungs were atelectatic, and congested with blood without oedema. Hepatic congestion was noted. Review of the lung slides by Dr Marlene Rabinovitch, Stanford University, California, revealed massive hypertensive mural changes in the large pulmonary arteries. The specimens proved unsuitable for evaluation of the peripheral vessels.

Discussion

The questions raised by our experience are the cause of death of our patient, and its avoidability. Apart from the respiratory symptoms, there were no other signs of disease that could have precipitated the deterioration. Death occurred suddenly and unexpectedly.

Mechanism of death

Lesions permitting intraatrial shunting are known to be associated with microatelectasis.[3] Respiratory symptoms after anaesthesia, and the atelectasis noted at autopsy, suggest that some areas of the lung may have been poorly ventilated. The girl needed oxygen to maintain acceptable saturations. The epoprostenol we administered may have improved the flow of blood to the lungs, but lacking selectivity for ventilated lung areas, may have resulted in a mismatch of ventilation and perfusion. Such mismatch is well described during treatment of primary pulmonary hypertension[4] using epoprostenol, as it is in congenital cardiac disease.[5] To our knowledge, as yet there are no deaths ascribed to this mechanism in children with congenital cardiac disease, but we believe that mismatch between ventilation and perfusion was of major importance in our patient. Right ventricular failure, and myocardial ischaemia due to terminal desaturation, may also have contributed to the negative outcome. The hazard of rebound pulmonary hypertensive crisis from interruption of epoprostenol treatment is well recognised.[6] We are not aware, however, of reports of rebound effects related to the withdrawal of sildenafil, and this seems unlikely in our case.

Alternative options for treatment

We are aware that our patient would have been offered primary surgical intervention in some centres. The combination of pulmonary hypertension with exclusively atrial shunting, however, is rare in infancy. It indicates a strong genetic predisposition, and possibly represents primary pulmonary vascular disease.[7] In the presence of pulmonary hypertension, surgical closure of interatrial communications is associated with high risk[8] and the benefit is debatable.[7] Based on anecdotal reports, and the availability of the drug, we used an oral mixture of sildenafil made from tablets in our pharmacy. The dosage of epoprostenol was in accordance with the recommendations of Rosenzweig et al.[1]

Monitoring patients during therapy

In our patient, the blood pressure and rate of respiratory remained unchanged. Transcutaneous measurements of the saturations of oxygen revealed transient reductions. None of these tests were suggestive of serious complications until the sudden episode of hypoventilation. Echocardiography is difficult to interpret in a non-collaborating child. Subtle changes in the flow of blood to the lungs may pass undetected. Mismatch between ventilation and perfusion is also difficult to monitor. Elevations in right atrial pressure may indicate right ventricular failure, while invasive monitoring of central venous pressure could be useful. We had chosen a thin single-lumen catheter, and central venous pressure could not be measured without stopping the infusion.

Whether the subjective improvement on sildenafil was significant is an unresolved question. Repeated catheterization could perhaps have shown any effects on pulmonary vascular resistance or flow. Invasive investigations themselves, however, are not without risk, and are difficult to interpret under general anaesthesia. In older children, exercise testing would be an appropriate investigation.

Conclusions

Treatment of pulmonary hypertension in children with congenital cardiac disease remains experimental. Individual differences may occur in the response to various pharmacological agents. Caution is needed when starting, stopping, or changing pharmacological treatment even when effects seem small. Careful monitoring is of paramount importance. Mismatch between ventilation and perfusion may obscure the clinical picture, and should be carefully considered. There is a strong need to establish and agree protocols for treatment.

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