Successful Opening of Ductus Arteriosus with Milrinone in a Newborn with Tetralogy of Fallot and Pulmonary Atresia

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Introduction

Milrinone, an inhibitor of bipyridine phosphodiesterase (PDE) III, increases the level of cyclic adenosine monophosphate (cAMP), reinforces cardiac muscle contraction, and induces vasodilation. It has been used for the management of heart failure and persistent pulmonary hypertension of the neonate (PPHN). Both we and other researchers have reported that infants administered milrinone have significantly larger patent ductus arteriosus (DA) diameters after the infusion was commenced.

Tetralogy of Fallot (TOF) assumes its' most severe form when accompanied by pulmonary atresia (PA). Preserving the patent ductus arteriosus to maintain pulmonary blood flow is life-saving for patients with this congenital heart disease. Milrinone, a selective phosphodiesterase III inhibitor, is a potent vasodilator. Here, we report the successful use of milrinone for a newborn infant with TOF and PA for keeping the ductus arteriosus open and thereby maintaining pulmonary circulation. Milrinone is a useful drug because of its inotropic, lusitropic, and pulmonary vasodilating effects, in addition to its ability to keep the ductus arteriosus open and its relatively mild side-effects. Case series and comparative studies will be needed in the future to verify the effectiveness of this drug.

Key Words: Congenital heart disease, Tetralogy of Fallot, Pulmonary atresia, Ductus arteriosus, Milrinone, Phosphodiesterase inhibitor, Newborn

Case report

A male newborn weighing 3,330 g was delivered by a Caesarean section at 38 weeks of gestation. A possibility of ventricular septal defect (VSD) and anomalies of the great arteries were recognized in utero. The Apgar scores were 8 at 1 min and 9 at 5 min. The initial oxygen saturation recorded by pulse oximetry (SpO₂) was 72%, and it elevated gradually to 85% by 10 min after birth. The blood pressure (BP) was 59/27 mmHg and the heart rate was 152/min on...
admission.

The infant had no abnormalities in the head, neck, abdomen, limbs, or genitalia. The neurologic findings were within the normal ranges. Postnatal echocardiography showed large VSD and overriding of the aorta (fig. 1) with PA (fig. 2) and a patent DA. The main pulmonary artery was not properly developed. However, the left and right pulmonary arteries were normal in size (fig. 3). No collateral vessels were found, and no other specific abnormalities were found on abdominal or cranial ultrasonography. The laboratory tests on admission revealed hematocrit of 47%, white blood cell count of 12,740/mm³, platelet count of 202,000/mm³, aspartate aminotransferase (AST) of 24 U/L, alanine aminotransferase (ALT) of 6 U/L, blood urea nitrogen (BUN) of 8.6 mg/dL and creatinine (Cr) of 0.5 mg/dL.

Milrinone was administered continuously via percutaneous central venous catheter (PCVC) at an infusion rate of 0.375 µg kg⁻¹ min⁻¹. With the medication, the SpO2 remained between 90% and 92%. On day 3 of life, follow-up echocardiography showed an adequately open DA with the diameter of 3.8 mm (fig. 4). No desaturation, (i.e., SpO2 < 80%), was noted during milrinone infusion. During the infusion of milrinone, the heart rate ranged from 135/min to 155/min, systolic BP from 55 to 70 mmHg and diastolic BP

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![Fig. 1. Parasternal long axis view of the patient’s echocardiogram. Large VSD and overriding of the aorta was shown. The outlet of the right ventricle looked atretic. But the atretic valve was not evident. Only rudimentary main pulmonary artery could be visible (arrows). Abbreviations: LA, left atrium; LV, left ventricle; Ao, aortic root; RV, right ventricle; VSD, ventricular septal defect.](image1)

![Fig. 2. Subcostal anatomical view of the patient’s echocardiogram. By tilting the probe upward, the atretic pulmonary valve (arrow) was visible. The patient was diagnosed as TOF with PA. Abbreviations: LV, left ventricle; RA, right atrium; RV, right ventricle.](image2)

![Fig. 3. Parasternal short axis view of the patient’s echocardiogram. The diameters of the left and right pulmonary arteries were 4.1 mm and 4.6 mm, respectively. Abbreviations: LPA, left pulmonary artery; Ao, Aorta; RPA, right pulmonary artery.](image3)

![Fig. 4. Parasternal short axis view of the patient’s echocardiogram showing the patent ductus arteriosus. The ductus arteriosus was well maintained patent with the diameter of 3.8 mm during the continuous infusion of milrinone. Abbreviation: PDA, patent ductus arteriosus.](image4)
from 30 to 42 mmHg. The results of the laboratory tests on day 4 of life revealed hematocrit of 39.9%, white blood cell count of 9,100/mm³, platelet count of 255,000/mm³, AST of 34 U/L, ALT of 15 U/L, BUN of 5.1 mg/dL, and Cr of 0.2 mg/dL. There were no side effects of milrinone, such as fluctuation of BP, tachycardia, dysrhythmia, thrombocytopenia, or changing of the renal function, during the infusion. On day 5 of life, the patient was transferred to a cardiac surgeon for a shunt operation.

**Discussion**

In TOF with PA, the pulmonary valve is atretic, and the pulmonary trunk may be hypoplastic or atretic as well. As the pulmonary valve is atretic, the entire right ventricular output should be ejected into the aorta. To maintain the pulmonary blood flow, collateral vessels, such as major aortopulmonary collateral arteries (MAPCAs) or a patent DA, should be needed. The degree of development of the branch pulmonary arteries decides the ultimate prognosis. If both of branch pulmonary arteries are severely hypoplastic and fail to grow after a palliative shunt procedure like Blalock-Taussig shunt, heart-lung transplantation may be the only option.

The DA is a normal and essential fetal structure. Abnormalities develop if it remains patent after the neonatal period. In fetal life, the most important factors for patency of the DA are a relatively low fetal oxygen tension and cyclooxygenase-mediated products of arachidonic acid metabolism (primarily prostaglandin [PGE₂] and prostacyclin [PGI₁]). PGE₂ and PGI₁ are produced locally and circulating in the fetus, PGE₂ and PGI₁ cause vasodilation of the DA by interacting with ductal prostanooid receptors. The production of PGE₂ and PGI₁ is increased by the placenta. Also, their degradation is decreased in the fetal lung. Both of the mechanisms make the levels of circulating PGE₂ and PGI₁ high in the fetus.

In newborns with various forms of PA, pulmonary blood flow can be almost entirely absent. Therefore, keeping the DA open is critical. Alprostadil, a potent vasodilator also known as prostaglandin EL₁, is the most common drug used to maintain DA patency. The side-effects of alprostadil include fever, hypotension, rhythm disturbance, inhibition of platelet aggregation, cortical proliferation of long bones with long-term infusion, apnea, and sudden cardiac arrest.

For the current patient, we chose milrinone to maintain pulmonary circulation via the DA to avoid the side-effects of alprostadil. The size of the DA remained the same, and the SpO₂ was stable during milrinone infusion in this patient, with no side-effects.

The effects of PDE inhibitors include increasing intracellular cAMP levels and cardiac contractility, inducing mild systemic vasodilation, and reducing myocardial oxygen consumption. PDE inhibitors induce vasodilation by delivering calcium to the sarcoplasmic reticulum. They have an inotropic effect mediated by the trans-sarcosomal flow of calcium. Further, they exhibit a lusitropic effect by promoting the dissociation of the actin-myosin complex. Milrinone is a selective PDE III inhibitor that has been reported to induce vasodilation of the pulmonary vessels in the PPHN. The side-effects of milrinone in infants include arrhythmia, fluctuation of BP, derangement of the renal function, and thrombocytopenia. None of these side-effects were found in the present case.

In a randomized trial of milrinone versus a placebo for the prevention of low systemic blood flow in very preterm infants, the infants randomized for milrinone had significantly larger DA diameters after infusion was commenced. The overall incidence of patent DAs treated with indomethacin was 81% for the milrinone group and 69% for the placebo group, and this difference was not significant. In one animal study, milrinone was found to dilate the DA postnatally in a dose-dependent manner. Further, it prevented indomethacin-induced fetal DA constriction. We have previously reported the use of milrinone for the treatment of PPHN. We have also been using milrinone for pulmonary hypertension, and have found that the DA opens widely after milrinone infusion. In several cases, we effectively used milrinone to keep the DA open in TOF patients (not published). But, there has been no report of the use of
milrinone for the purpose of opening the DA. To the best of our knowledge and according to a literature review, this is the first report of the successful use of milrinone in a neonate with TOF and PA.

Milrinone improves pulmonary hypertension in PPHN patients and the low-cardiac-output state in infants after cardiac surgery. Recently, it has been shown to be useful in the management of postsurgical duct ligation myocardial failure. For preterm and term infants, very limited reported data is available on the role of milrinone in improving circulation. One study showed that milrinone did not prevent low systemic blood flow during the first 24 hours in very preterm infants. Milrinone has been recommended for use in preterm infants who have normal blood pressure but low cardiac output, because of its effects in decreasing afterload and improving cardiac contractility. Milrinone might effectively maintain DA patency, increase pulmonary circulation by dilating the pulmonary vessels, and restore cardiac output by improving cardiac contractility and reducing the afterload. Therefore, we believe that milrinone may be more beneficial for certain congenital heart diseases for which maintaining DA patency is critical, such as TOF and PA, as in the present case.

We report a successful case of maintaining the patency of DA in a newborn with TOF and PA. Milrinone might be effective for treating certain types of congenital heart diseases that require DA patency to be maintained for adequate pulmonary blood flow. Its advantages could be its inotropic and lusitropic effects and its pulmonary vaso-dilatory effects, along with limited severe side-effects. To confirm the efficacy of milrinone, further case series and comparative studies are needed in the future.

References