Levosimendan

Levosimendan is a phosphodiesterase III inhibitor as well as a "calcium-sensitizer." As a calcium-sensitizer, it improves myocardial contractility by binding to Troponin C and stabilizing its interaction with calcium. Unlike other calcium sensitizers, that may worsen diastolic function, levosimendan also has lusitropic properties because its binding to Troponin C is dependent on cytosolic calcium concentrations. Additionally, its partial phosphodiesterase inhibition results in lusitropy and vasodilation. Myocardial contractility in the newborn is more dependent on calcium compared to adults.[1] Thus, levosimendan may be useful in neonates. However, the effect of levosimendan may differ following asphyxia. In an asphyxiated piglet model, levosimendan increased cardiac output without an increase in carotid and mesenteric flow but with increased estimated PVR.[2] In another asphyxiated piglet model, comparing milrinone and levosimendan (both combined with dopamine), milrinone increased mesenteric perfusion and reduced myocardial oxidative stress compared to levosimendan.[3] There are case reports and small case series noting successful use of levosimendan in neonates, including those with PPHN.[4,5] A recent case report of two neonates, levosimendan was chosen because the babies had risks or history of arrhythmia.[4] Overall levosimendan carries a lower risk of arrhythmia, except in high doses in patients with myocardial ischemia.[6]

Special considerations

Use of inotropes in infants of diabetic mothers with hypertrophic cardiomyopathy:

Infants born to mothers with diabetes (IDM) may have hypertrophic cardiomyopathy and impaired cardiac output that must be considered when choosing vasoactive medications. The echocardiogram of IDM often shows asymmetric septal hypertrophy, which can lead to left

ventricular outflow obstruction.[7] Traditionally the management involves β-blockade. Thus, catecholamine infusions may cause increased inotropy and/or chronotropy that further increase left ventricular outflow obstruction or impair cardiac output. Milrinone, however in conjunction with β-blockade, may provide improved cardiac output and oxygenation due to its inotropic effect without chronotropy and its lusitropy and vasodilatory properties.[8] A fluid bolus followed by a vasopressor with minimal cardiac inotropic activity (such as vasopressin) may also be considered in these situations.

Extracorporeal Life Support (ECLS)

Extracorporeal life support (ECLS) is also a treatment option for newborns with PPHN. Particularly, it is used for patients that have labile hemodynamics despite vasoactive infusions, and that have poor oxygenation despite pulmonary vasodilator therapy and ventilator management. Additionally, the potential benefit of ECLS is to avoid toxic ventilator settings or iatrogenic effects from other therapies such as high FiO_2 or high dose vasoactive infusions. While therapies such as iNO have decreased the need for ECLS in patients with PPHN and meconium aspiration syndrome (MAS), the overall annual ECLS runs for PPHN over the last 25 years has remained relatively unchanged.[9] In fact, PPHN remains the third most common reason for neonatal ECLS following MAS and then CDH (although MAS and CDH can cause PPHN). Additionally, the survival rates of ECLS for PPHN have been relatively unchanged (~72%).[9]

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