Milrinone Use to Treat Persistent Pulmonary Hypertension of the Newborn

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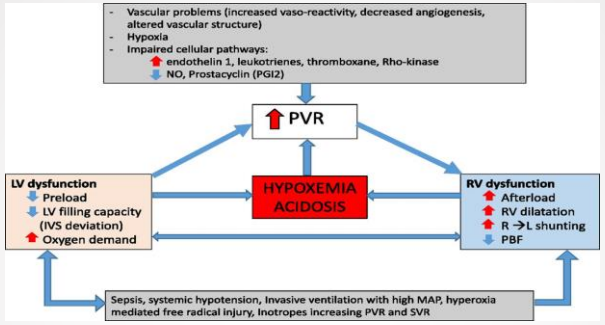
Abstract

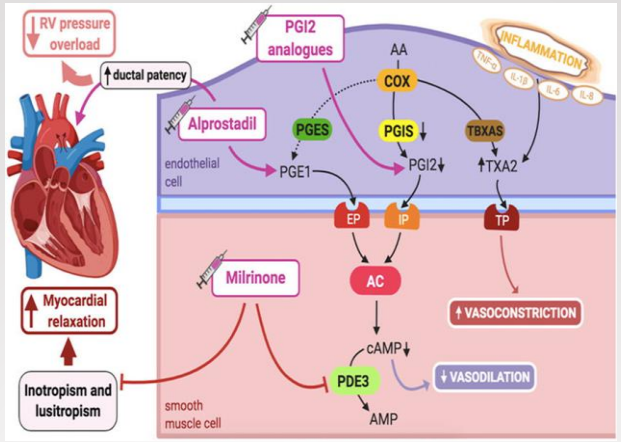
The use of inhaled nitric oxide (iNO) in the treatment of persistent pulmonary hypertension of the newborn (PPHN) is well recognized and supported by the literature. **Statement of the Problem:** A high percentage of infants treated with iNO may exhibit a temporary response, to no improvement in oxygenation. Furthermore, iNO is not readily available in many neonatal intensive care units due to its high cost. **Methodology:** A literature review was conducted using Cumulative Index of Nursing and Allied Health Literature (CINAHL) Complete to identify recent studies in the last 5 years (2015-2020) supporting the use of milrinone in the management of PPHN when iNO treatment fails or is unavailable. **Conclusion:** Milrinone's inotropic and lusitropic effects are promising in the treatment of PPHN, especially in cases where PPHN is accompanied by ventricular dysfunction. Small trials and case reports indicate milrinone can act synergistically with iNO to treat PPHN, especially in infants who present with ventricular dysfunction. Milrinone has also shown to decrease the amount of time infants spent on invasive ventilation with iNO. However, larger randomized controlled trials are needed to provide more data on milrinone's use in the treatment for PPHN.

PPHN is a syndrome characterized by persistent elevation of pulmonary vascular resistance and hypoxemia due to right-to-left extrapulmonary shunting of blood across the ductus arteriosus or foramen ovale. (Bendapud, et al., 2015; Pedersen, et al., 2018). iNO is the treatment of choice for PPHN, however, However, about 40% of infants are resistant to iNO (El-Khuffash et al., 2018; Martinho, Adão, Leite-Moreira & Brás-Silva, 2020).



The myocardial dysfunction associated with PPHN is due to the reduced pulmonary venous return created by the increased pulmonary vascular resistance (PVR). This results in increased right ventricular (RV) afterload and reduced left ventricular (LV) preload, compromising the function of both right and left ventricles (Bendapudi et al., 2015).

Milrinone decreases pulmonary artery pressure and acts synergistically with iNO and inhaled prostanoids, improving pulmonary vasodilation and decreasing oxygen requirement in infants with PPHN (El-Khuffash et al., 2018; Martinho, Adão, Leite-Moreira & Brás-Silva, 2020).



Pathogenic mechanisms of persistent pulmonary hypertension of the newborn (PPHN) and its current and potential target therapies: Arachidonic acid-prostacyclin-cAMP pathway. AA, arachidonic acid; AC, adenylyl cyclase; AMP, adenosine monophosphate; cAMP, cyclic adenosine monophosphate; COX, cyclooxygenase; EP, PGE1-receptor; IL-1β, IL-6, IL-8, interleukins-1β, 6 and 8; IP, PGI2-receptor; PDE3, phosphodiesterase-3; PGE1, prostaglandin E1; PGES, PGE1 synthase; PGI2, prostacyclin; PGIS, PGI2 synthase; RV, right ventricle; TBXAS, TXA2 synthase; TNF-α: tumor necrosis factor α; TP, TXA2-receptor; TXA2, thromboxane A2. Target therapies are marked with a syringe icon and are colored based on the type of evidence supporting its use on PPHN-Purple: Evidence on its was obtained by adequately powered RCTs/meta-analysis; Pink: Evidence limited to observational studies or small and underpowered RCTs and/or inconsistent results in human newborns; Blue: Beneficial effects only demonstrated in experimental models of PPHN.

Milrinone is indicated for use in infants with PPHN who have ventricular dysfunction, especially if associated with pulmonary venous hypertension, or elevated left atrial pressure. Vascular phosphodiesterase-3 (PDE-3) breaks down cAMP in arterial smooth muscle cells and myocardium. PDE3 inhibitors raise cAMP levels, promoting myocardial contractility and increasing right cardiac output, which reduces afterload, correcting the myocardial issues caused by high pulmonary vascular resistance (Bendapudi,et al, 2015).

Conclusion

Although larger randomized controlled trials are needed to provide more data on milrinone's use in the treatment for PPHN, data suggest milrinone's inotropic and lusitropic effects are promising in the treatment of PPHN, especially in cases where PPHN is accompanied by ventricular dysfunction (Fuloria & Aschner, 2017). Milrinone has also shown to decrease the amount of time infants spent on invasive ventilation with iNO (El-Khuffash, el al., 2018). Therefore, the neonatal nurse practitioner may consider using milrinone in infants who develop myocardial dysfunction due to PPHN, and who show poor response to iNO. Milrinone can potentially show the following effects:

- Improved response rate to iNO
- Reduced the time spent on iNO and mechanical ventilation
- Reduced length of stay, decrease in hospital costs in the NICU
- Considerable savings if the use of milrinone is successful in reducing time on iNO
- Reduce burdens on families

References:

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