Milrinone and Amrinone

Milrinone and Amrinone, the latter now renamed inamrinone, are phosphodiesterase 3 (PDE3) inhibitors indicated for acute management of decompensated heart failure. These drugs work by inhibiting PDE3, an enzyme located primarily in cardiac myocytes and vascular smooth muscle cells. This enzyme normally degrades cAMP, so blockade by milrinone and amrinone result in increased cAMP levels. This potentiates the effects of beta-1 and beta-2 adrenergic receptors which use cAMP as a second messenger. Increased cAMP levels result in increased cardiac inotropy and increased systemic vasodilation, leading to reduced afterload. These drugs can help manage acute decompensated heart failure as they help the heart contract more forcefully and with relatively less effort due to afterload reduction. Side effects can include ventricular arrhythmias and hypotension, so patients require close cardiopulmonary monitoring.



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Mechanism of Action

Phosphodiesterase 3 Inhibitor

Phosphorus-P Duster (3) Tree in Inhibiting-chains

Milrinone and Amrinone are phosphodiesterase 3 inhibitors. This enzyme is present primarily in cardiac myocytes and the smooth muscle cells of arteries and veins. It's responsible for breaking down cyclic adenosine monophosphate (cAMP). Inhibition of this enzyme will cause a rise in cAMP levels, which directly activate protein kinase A (PKA). In myocytes, increased cAMP leads to increased inotropy and therefore improved heart contractility. In the vessels, increased cAMP leads to vasodilation.

Potentiates Beta Receptor Effects

P-springs Beta Receptor

Milrinone and Amrinone potentiate the effects of beta adrenergic receptor stimulation. Both beta-1 and beta-2 receptors activate adenylyl cyclase when stimulated, increasing intracellular cAMP concentrations. Beta-1 and beta-2 receptors are stimulated by catecholamines like epinephrine and norepinephrine.

Inotrope

I-heart Flexing

Milrinone and Amrinone increase cardiac inotropy or contractility. Inhibition of cAMP degradation in cardiac myocytes increases the amount of available cAMP. cAMP activates protein kinase A, releasing calcium from the sarcoplasmic reticulum. Recall that calcium is required for muscle contraction, and that increased levels of calcium will reveal additional actin binding sites by moving troponin out of the way. Increased binding of myosin and actin then increases inotropy.

Vasodilator

Vase-dyed

Milrinone and Amrinone cause vasodilation in the systemic vasculature by acting on vascular smooth muscle cells. Preventing the degradation of cAMP leads to higher cAMP levels and activation of protein kinase A. This leads to increased phosphorylation of myosin light chain kinase which relaxes vascular smooth muscle, causing vasodilation. Systemic vasodilation decreases afterload, allowing the heart to pump more effectively.

Indication

Acute Decompensated Heart Failure

Acute-angle Decomposing Heart Dying

Milrinone and Amrinone can be used to treat acute decompensated heart failure and cardiogenic shock. In decompensated heart failure, the heart is unable to keep up with the workload imposed on it. This may be due to a variety of factors including fluid overload, cardiac ischemia or arrhythmias. Milrinone and amrinone increase the contractility of the heart while reducing afterload via systemic vasodilation, allowing the diseased heart to pump more effectively.

Side Effects

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Ventricular Arrhythmias

Vent-heart with Broken-Arrhythmia-drum

Milrinone and Amrinone have the potential to cause ventricular arrhythmias. Their cardiostimulatory effects combined with reflex tachycardia due to vasodilation can induce arrhythmias in a non-dose dependent fashion. As such, these drugs are typically only indicated for treatment of acute conditions, and require close cardiopulmonary monitoring.

Hypotension

Hippo-BP

Milrinone and Amrinone can cause hypotension. This response is dose dependent, and can be considered a continuation of the drug's therapeutic effects on the vasculature. Increased levels of these drugs in the bloodstream can cause vasodilatory effects greater than initially intended. For this reason, patients require continuous monitoring.

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