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Letter to Editor

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Reconsidering milrinone: Time to revive the oral form for drug repurposing?

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Milrinone, a selective phosphodiesterase-3 (PDE-3) inhibitor, was first introduced in the late 1980s as an intravenous (IV) treatment for acute heart failure. Around the same time, an oral formulation was also developed in hopes of helping patients manage chronic heart failure. However, clinical trials (most notably, the PROMISE study in 1991) revealed a concerning outcome: patients with severe chronic heart failure who used PDE-3 inhibitors experienced increased rates of both morbidity and mortality. These findings, along with the potential of the drug to trigger life-threatening ventricular arrhythmias, ultimately led to its oral formulation being withdrawn from routine clinical use.[1]

However, in light of emerging scientific evidence, milrinone appears to deserve renewed attention, not for cardiac conditions, but within the field of neurology and neurosurgery, particularly in the management of subarachnoid hemorrhage (SAH).[2] Moreover, other promising effects, such as anti-tumor effects, have also been reported for milrinone, mediated through the suppression of oncogenic pathways such as phosphatidylinositol 3'-kinase (PI3K)/protein kinase B (AKT), mitogen-activated protein kinase (MAPK), and wingless-related integration site/beta-catenin (Wnt/β-catenin) within the tumor microenvironment. Furthermore, it may reduce mitochondrial production of reactive oxygen species (ROS).[3-6]

In recent years, several studies have highlighted the beneficial effects of IV milrinone in acute cases of SAH.[2-5,7,8]

Beyond its direct vasodilatory effect via PDE-3 inhibition, the drug has demonstrated notable neuroprotective properties by reducing apoptotic process and enhancing anti-inflammatory and antioxidant mediators.[9]

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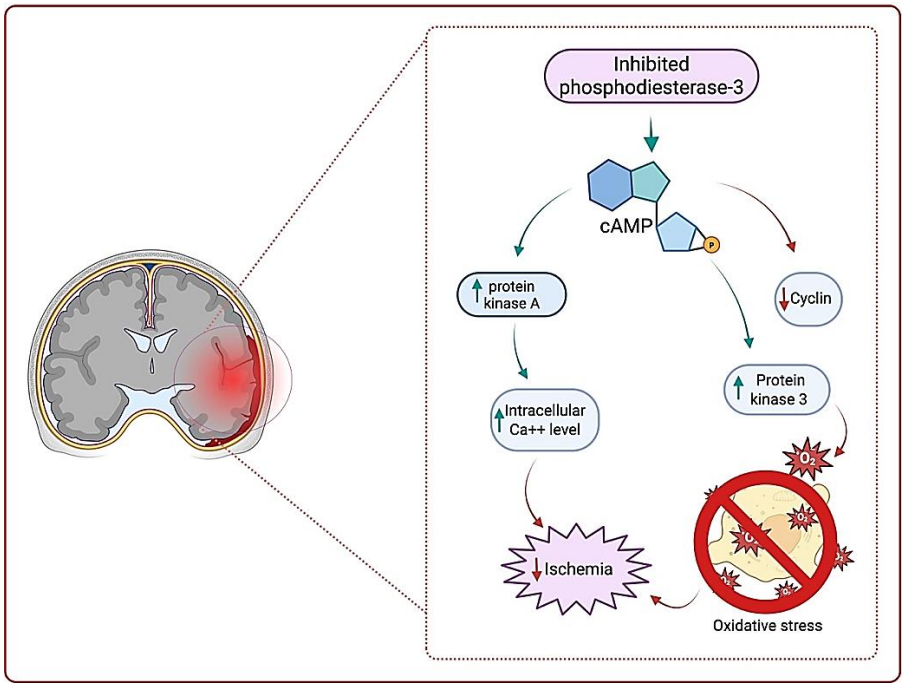

Figure 1. Inhibitory mechanism of milrinone in delayed ischemia
cAMP: Cyclic adenosine monophosphate

Mechanistically, PDE-3 inhibition increases intracellular cyclic adenosine monophosphate (cAMP) levels, which activates protein kinase A (PKA) and raises intracellular calcium concentrations.[10,11]

Additionally, elevated cAMP has been shown to reduce the expression of cell cycle-promoting factors such as cyclins and cyclin-dependent kinases, while enhancing pro-apoptotic signaling through pathways involving PKA and exchange protein directly activated by cAMP (EPAC); together, these effects contribute to reduced oxidative stress and ischemic injury (Figure 1).[6]

All of these mechanisms, among others, suggest that milrinone may be beneficial in the management of SAH, particularly by mitigating ischemic cascades, apoptotic processes, and delayed cerebral ischemia (DCI) associated with the condition.

Given the successful use of intra-arterial (IA) and IV milrinone in the management of SAH, as demonstrated in studies,[2,12] is not it time to also reconsider the potential of its oral formulation, not for heart failure, but for addressing DCI following SAH? Perhaps, much like the story of nimodipine, oral milrinone deserves renewed investigation in this context.

The potential benefits of oral milrinone in the long-term management of patients with a history of chronic SAH (for example, during the recovery phase or for the prevention of delayed vasospasm) deserve thoughtful consideration. Currently, there is no specific short- or long-term treatment for SAH. The administration of IV nimodipine during the initial phase of vasospasm, followed by oral continuation for several weeks, has not shown a significant impact on survival or mortality reduction. Therefore, incorporating oral milrinone – together with agents such as statins, melatonin, and magnesium, alongside nimodipine – may offer potential benefits.

Nonetheless, concerns about cardiovascular side effects, particularly in patients with underlying cardiac conditions, must be carefully evaluated.

Finally, our perspective on pharmacological agents may need to evolve beyond their historical indications. Drug once set aside due to increased morbidity and mortality in a specific context might prove to be life-saving in another, provided that the dosage, route of administration, and formulation (e.g., nano-drug delivery or targeted therapy) are appropriately adjusted.

This pattern is evident in drugs such as amantadine and thalidomide, which found renewed therapeutic value despite their adverse effect profiles. In the case of oral milrinone, any potential reintroduction should be guided by well-designed clinical trials and a rigorous risk-benefit assessment within the framework of modern neurology.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

None.

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