The use of milrinone for curing a chronic heart failure.

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Abstract- **Phosphodiesterase inhibitors such as milrinone can relieve symptoms and improve hemodynamics in patients with advanced congestive heart failure. We retrospectively evaluated the hemodynamic and clinical outcomes of long-term combination therapy with intravenous milrinone and oral β-blockers in 65 patients with severe congestive heart failure (New York Heart Association class IV function and ejection fraction <25%) refractory to oral medical therapy. Fifty-one patients successfully began β-blocker therapy while on intravenous milrinone. Oral medical therapy was maximized when possible. The mean duration of milrinone treatment in this combination-treatment group was 269 days (range, 14–1,026 days). Functional class improved from IV to II–III with milrinone therapy. Twenty-four such patients tolerated β-blocker up-titration and were successfully weaned from milrinone. Sixteen patients (31%) died while receiving combination therapy; one died of sudden cardiac death (on treatment day 116); the other 15 died of progressive heart failure or other complications. Hospital admissions during the previous 6 months and admissions within 6 months after milrinone initiation stayed the same. Meanwhile, the total number of hospital days decreased from 450 to 380 (a 15.6% reduction), and the mean length of stay decreased by 1.4 days (a 14.7% reduction).**

We conclude that 1) milrinone plus β-blocker combination therapy is an effective treatment for heart failure even with β-blocker up-titration, 2) weaning from milrinone may be possible once medications are maximized, 3) patients' functional status improves on the combination regimen, and 4) treatment-related sudden death is relatively infrequent during the combination regimen.

Index Terms- **Adrenergic beta-antagonists, heart failure, congestive, milrinone**

I. INTRODUCTION

Milrinone is a medication indicated for cardiac support in patients with acute heart failure, pulmonary hypertension, or chronic heart failure. It functions by improving cardiac contractility (inotropy), cardiac relaxation (lusitropy), and inducing vasodilation and has the overall effect of increased cardiac output, improvement of left ventricle-arterial coupling, and enhanced cardiac mechanical efficiency. Its use is primarily in the perioperative and ICU settings, although it also has utility for outpatient therapy in select patient populations. This activity will review its mechanism of action, its indications, and the potential harm and benefits associated with its use. It will also discuss its role throughout various specialties of medicine, including ICU care, perioperative care, use in pediatric populations, and the now discontinued use in the outpatient setting as an oral medication.

II. OBJECTIVES

- Describe the mechanism of action of milrinone.
- Identify conditions that indicate milrinone therapy.
- Summarize the potential adverse effects associated with milrinone.
- Explain why the use of milrinone requires thoughtful planning and discussion throughout the interprofessional team with other professionals and specialists involved

in the patient's perioperative, ICU, and outpatient care.

Indications

Milrinone is a medication indicated for cardiac support in patients with acute heart failure, pulmonary hypertension, or chronic heart failure. It functions by improving cardiac contractility (inotropy), cardiac relaxation (lusitropy), and inducing vasodilation and has the overall effect of increased cardiac output, improvement of left ventricle-arterial coupling, and enhanced cardiac mechanical efficiency. Its use is primarily in the perioperative and ICU settings, although it also has utility for outpatient therapy in select patient populations.[1]

Use in the Perioperative Setting

Milrinone is often used during various cardiac surgeries, including coronary artery bypass graft surgery, cardiac transplantation, and other cardiac surgeries that require cardiac support. Likewise, it has utility in non-cardiac surgeries for patients with acute decompensated left ventricular heart failure, acute right ventricular heart failure, or pulmonary artery hypertension.

Cardiac Units and the ICU

Milrinone use is mostly in the ICU and the cardiac unit for cardiac support in patients in acute heart failure, for weaning patients with pre-existing left ventricular dysfunction from cardiopulmonary bypass, or as a temporizing agent for patients with plans to undergo cardiac surgery or transplantation. In the neonate population, it is indicated to treat persistent pulmonary hypertension (i.e., neonates with a congenital diaphragmatic hernia).

Outpatient Use of Milrinone

Clinicians direct the use of milrinone in the outpatient setting to patients who have severe symptoms of congestive heart failure (CHF) refractory to optimal medical therapy. Previously, an oral version was in use in the outpatient setting for symptomatic treatment of New York

Association (NYHA) class III/IV CHF; however, this fell out of favor due to increased patient mortality secondary to ventricular arrhythmia and sudden cardiac death.[2] (see Toxicity section)

In pediatric patients with congenital heart failure, outpatient milrinone infusion regimens are a means of bridging patients until they can undergo cardiac transplantation, initiate mechanical circulatory support, or it may work palliatively in those that are not eligible for transplant/mechanical intervention. This method of treatment is effective for improving patient symptoms and decreasing the number of hospitalizations.

Mechanism of Action

This section discusses the pharmacology of milrinone.

Phosphodiesterase Inhibition

Milrinone is the phosphodiesterase inhibitor drug class. Phosphodiesterase is an enzyme that hydrolyzes the second messenger cyclic adenosine monophosphate (cAMP) and guanosine monophosphate (cGMP), terminating their effects in various tissues. There are several variants of phosphodiesterase enzymes throughout the body; milrinone is selective for phosphodiesterase III at low doses and nonselective at high doses. Phosphodiesterase III is located primarily in the cardiac sarcoplasmic reticulum and smooth muscle in arteries and veins.

Cardiac Effects of Milrinone

In the myocardium, PDE III inhibitors lead to increased contractility (inotropy) and improved relaxation (lusitropy), which improves systolic and diastolic function, thereby optimizing cardiac output. Increased heart rate (chronotropy) also occurs but is less pronounced than the increases in heart rate seen with medications in the catecholamine class.

Inhibition of phosphodiesterase III prevents the breakdown of cAMP with downstream effects of increasing protein kinase A activity, which causes phosphorylation of calcium ion channels in the

sarcoplasmic reticulum and ultimately increases calcium availability to the myocyte sarcomere. This increased calcium availability manifests in increased cardiac inotropy and chronotropy.

PDE III inhibition causes increased calcium reuptake into the sarcoplasmic reticulum, which results in enhanced myocardial relaxation (lusitropy) with producing improved diastolic function.

Vasoactive Effects of Milrinone

In the vasculature, PDE III inhibition prevents cGMP metabolism in the smooth musculature and results in vasodilation in both arteries and veins. The vasodilatory effects seen with milrinone are more potent than those seen with beta-2 agonists, including dobutamine and isoproterenol. Milrinone is available in an inhalational formula for directed vasodilation of the pulmonary vasculature to treat pulmonary hypertension.

Advanced heart failure is an increasingly prevalent problem in cardiology. As the population ages and therapy for coronary artery disease improves, more people are developing advanced congestive heart failure (CHF). The annual mortality rate of patients who have New York Heart Association (NYHA) functional class IV CHF remains high regardless of therapy with digitalis, angiotensin-converting enzyme (ACE) inhibitors, diuretics, and β-blockers. 1 In a growing number of patients, symptoms of NYHA class IV CHF persist despite maximal oral medical management. The estimated mortality rate for such patients would exceed 40% were it not for therapies such as transplantation and support with left ventricular assist devices. In comparison, the recent COPERNICUS trial 2 revealed an annual mortality rate of 19.7% for its control patients (a somewhat healthier patient population [NYHA class III–IV]) who received oral medical therapy; other studies have found mortality rates of >30% in patients treated with various inotropic agents. 3–6

Inotropic drug therapy for patients who have advanced heart failure has been shown to increase cardiac output, reduce preload and afterload, and have life-saving potential. 7 During the past 10 years, the positive inotropic agent and phosphodiesterase III inhibitor milrinone has been used intravenously to treat patients with acute heart failure and as a bridge to transplantation. 3,8,9 More recently, intravenous (IV) milrinone has shown promise as long-term therapy for CHF on an outpatient basis. 3 Milrinone can dramatically improve the functional status of patients with severe heart failure and improve end-organ function. Nonetheless, long-term milrinone administration is controversial. This is due mainly to results of the PROMISE trial, 10 a study from the pre-β-blocker era that showed increased mortality rates for patients treated with large doses of oral milrinone. 10 The PROMISE trial, however, did not evaluate the use of milrinone intravenously, in lower doses, or with β-blockers. Currently, β-blockers are used to treat patients with NYHA class II–IV heart failure. However, hypotension and weakness may occur during the usual 6-week period of up-titration. This is problematic for NYHA class IV patients who are refractory to oral medical management, since their therapeutic options are few and their risk of death may increase without intermittent outpatient inotropic therapy. Therefore, in the present study, we examined whether IV milrinone might sufficiently stabilize and support cardiac function in patients with severe heart failure that is refractory to oral medical therapy during the addition and up-titration of β-blocker therapy.

III. PATIENTS AND METHODS

We retrospectively reviewed the cases of 65 patients with severe congestive heart failure (NYHA class IV symptoms) who were treated with continuous IV milrinone and β-blockers on an outpatient basis. The demographics and characteristics of this patient population are shown in Table I. All patients were stabilized in the hospital first with a continuous IV infusion of low-dose milrinone (0.375–0.45 μg/kg per min) and later with β-blockers. A peripherally inserted central catheter was used to administer the milrinone, except in 1 patient who required a subclavian catheter. All patients had been unresponsive to the maximum oral dosages of digitalis, diuretics, and ACE inhibitors and could not be weaned from milrinone while in the hospital. Of these 65 patients, 14 could not tolerate the lowest dose of β-blocker and were sent home without β-blocker therapy. In the 51 patients who tolerated low doses of β-blocker in the hospital, up-titration was implemented on an outpatient basis every 3–4 weeks

(more slowly than the standard recommended rate of every 2 weeks). All patients were followed up in a specialized heart failure clinic.

Table thumbnail
TABLE I. Patient Characteristics by Treatment Regimen (n = 65)

In all cases, early weaning from milrinone during initial hospitalization was attempted but failed; failure was manifested clinically by an increase in symptoms of CHF. Later, weaning was considered for those patients who achieved NYHA class I–II function while on IV milrinone therapy and who tolerated β-blocker up-titration. Weaning consisted of discontinuing milrinone for 12 hours every other day for 1 week and then for 12 hours every day for 1 week. If the patient remained clinically stable, milrinone was discontinued after the 2-week period. If the patient did not remain clinically stable, weaning was implemented more slowly or for fewer hours per day.

Statistical methods are as follows: for all variables, differences between the 2 groups were considered statistically significant if the 2-tailed probability value was <0.05.

REFERENCES

1. Mody BP, Khan MH, Zaid S, Ahn C, Lloji A, Aronow WS, Gupta CA, Levine A, Gass AL, Cooper HA, Lanier GM. Survival With Continuous Outpatient Intravenous Inotrope Therapy in the Modern Era. Am J Ther. 2020 Oct 01;

2. Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM, Hendrix GH, Bommer WJ, Elkayam U, Kukin ML. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. N Engl J Med. 1991 Nov 21;325(21):1468-75.

3. Curley M, Liebers J, Maynard R. Continuous Intravenous Milrinone Therapy in Pediatric Outpatients. J Infus Nurs. 2017 Mar/Apr;40(2):92-96.

4. Dobashi S, Watanabe I, Nakanishi R, Hisatake S, Kiuchi S, Kabuki T, Oka T, Fujii T, Ikeda T. Comparing the effects of milrinone and olprinone in patients with congestive heart failure. Heart Vessels.

5. Ginwalla M, Tofovic DS. Current Status of Inotropes in Heart Failure. Heart Fail Clin.

6. Holmes CL, Walley KR. Vasoactive drugs for vasodilatory shock in ICU. Curr Opin Crit Care. 2009

7. Chong LYZ, Satya K, Kim B, Berkowitz R. Milrinone Dosing and a Culture of Caution in Clinical Practice. Cardiol Rev. 2018

8. Samiee-Zafarghandy S, Raman SR, van den Anker JN, McHutchison K, Hornik CP, Clark RH, Brian Smith P., Best Pharmaceuticals for Children Act—Pediatric Trials Network Administrative Core Committee. Safety of milrinone use in neonatal intensive care units.

9.Charisopoulou D, Leaver N, Banner NR. Milrinone in advanced heart failure: dose and therapeutic monitor outside intensive care unit. Angiology

10. Mladěnka P, Applová L, Patočka J, Costa VM, Remiao F, Pourová J, Mladěnka A, Karlíčková J, Jahodář L, Vopršalová M, Varner KJ, Štěrba M., TOX-OER and CARDIOTOX Hradec Králové Researchers and Collaborators. Comprehensive review of cardiovascular toxicity of drugs and related agents. Med Res Rev.

11.Burniston JG, Ellison GM, Clark WA, Goldspink DF, Tan LB. Relative toxicity of cardiotonic agents: some induce more cardiac and skeletal myocyte apoptosis and necrosis in vivo than others. Cardiovasc Toxicol.