Intravenous Milrinone in Cardiac Surgery

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Phosphodiesterase inhibitors including milrinone produce positive inotropic effects by slowing the hydrolysis of cyclic adenosine monophosphate in the myocardium. With a loading dose of 50 \( \mu \text{g/kg} \) followed by an infusion of 0.5 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \), milrinone increases stroke volume index and left ventricular velocity of circumferential fiber shortening after weaning from cardiopulmonary bypass. Milrinone has potential for the treatment and prevention of internal mammary artery spasm because of its vasodilative effect, which is similar to that of papaverine, and is a potent pulmonary vasodilator for patients with right ventricular dysfunction and pulmonary vasoconstriction. Low-dose milrinone may have anti-inflammatory properties and potentially can improve splanchnic perfusion.


Methods

A search of the MEDLINE database from 1975 to 2000 was conducted to identify pertinent articles using the keywords milrinone and cardiac surgery combined. The search was restricted to the English-language literature. The resulting articles were then further sorted to identify those most relevant to the topic. No specific criteria were used to make the final selection of the articles cited in this review, although every effort was made to recognize conflicting data and opinions.

Results

A total of 310 articles were identified that contained the combined search terms milrinone and cardiac surgery. From these 310 articles, the authors identified 42 that were deemed most relevant to cardiac surgery and used them as the basis for this review. An overview of the characteristics of milrinone and evidence of its use in cardiac surgery follows.

Characteristics and Use of Milrinone

Clinical Pharmacology

Compared with the catecholamines, milrinone has a longer half-time, necessitating a loading dose as well as a continuous infusion. During the first 12 hours of administration, drug disposition is determined largely by redistributional processes. As the length of administration increases, the effective half-time becomes more prolonged as tissue stores are saturated. The effective half-time is 36 minutes after 30 minutes of administration and increases to 138 minutes after 10 hours of administration [6]. For infusions lasting less than 10 hours, the half-time after discontinuation is less for milrinone than amrinone. The stability of milrinone has been demonstrated in the presence of 29 commonly used critical-care drugs and four intravenous solutions [7].

Milrinone has been shown to significantly increase cardiac index (CI) in patients with chronic CHF in a dosem-related manner, with plasma concentrations ranging from 66 to 427 ng/mL [8]. In cardiac surgical patients, Bailey and associates [4] reported that a milrinone loading dose of 50 \( \mu \text{g/kg} \) followed by a continuous infusion of 0.5 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) produced plasma milrinone concentrations in excess of 100 ng/mL and maintained thera-
peutic concentrations during weaning from cardiopulmonary bypass (CPB) and throughout the postoperative period. The plasma concentration associated with a 50% increase in CI was 167 ng/mL. The regimen of a 50–μg/kg loading dose plus an 0.5–μg · kg⁻¹ · min⁻¹ infusion achieves plasma levels of 100 to 300 ng/mL, thus bracketing this concentration that will produce 50% of maximum response and exceeding the threshold for substantial hemodynamic effect.

Clinical Effects
In clinical trials, milrinone increased load-dependent indices of contractility (maximum rate of rise of left ventricular [LV] pressure) in a dose-dependent fashion in patients with CHF [9, 10]. In patients with CHF, milrinone was not shown to increase myocardial oxygen consumption [11]. Direct intracoronary infusions of 50 μg/min of milrinone in patients with severe CHF have been shown to enhance contractility, increase stroke volume, decrease LV end-diastolic pressure, and decrease heart rate [9]. In healthy volunteers, a 30– to 60–μg/kg loading dose of milrinone followed by maintenance infusions to obtain plasma levels of 81 to 261 ng/mL caused significant decreases in diastolic arterial pressure (−12%), mean arterial pressure (−11%), and LV end-diastolic dimension (−5%). In addition, significant increases in LV fractional shortening (+14%) were obtained [12]. Significant decreases in LV end-systolic dimension (−11%) and LV end-systolic wall stress (−32%) and a decrease in calculated systemic vascular resistance (−10%) were also observed. Contractility indices were linearly related to plasma milrinone concentrations. Milrinone produced a dose-dependent increase in the velocity of circumferential fiber shortening caused by decreased afterload and enhanced contractility.

In vascular smooth muscle, cAMP causes a decrease in intracellular calcium concentrations. In addition to its effect on the myocardium, milrinone causes smooth muscle relaxation and vasodilation. These effects result in decreases in mean arterial pressure, central venous pressure, and pulmonary artery occlusion pressure as well as increases in cardiac output (CO) owing to afterload reduction [3, 9–13]. It has been clearly demonstrated, using load-independent indices of cardiac function, that milrinone has a positive inotropic effect [12]. However, the increase in CO after milrinone administration may be as much due to afterload reduction as to increased inotropic state. The possibility of an increase in CO as the result of enhanced inotropic state and afterload reduction may be attenuated by decreased preload and, in a worst case scenario, coronary hypoperfusion owing to hypotension. Excessive vasodilation may require fluid administration, vasopressors, or both. The vasodilating effects of milrinone have been shown to be dose dependent in patients with severe CHF [6].

Milrinone also affects diastolic function in patients with CHF, reducing diastolic pressure at any given diastolic volume while elevating maximum rate of rise of LV pressure (18%) and decreasing mean aortic pressure (11%) [13]. No changes occurred in peak LV systolic pressure. In addition, the peak LV filling rate increased by 42%, even though pulmonary artery occlusion pressure decreased.

Use in Cardiac Surgical Patients After CPB
Catecholamines are frequently administered to facilitate separation from CPB and to maintain an adequate CO postoperatively in the cardiac surgical patient. The mechanism of action of catecholamines is stimulation of cAMP production. Milrinone potentiates action of these agents by inhibiting the breakdown of cAMP. This may be particularly important in patients who were in CHF prior to operation, as β₁-adrenergic receptors can be down-regulated in this population. Therefore, when ventricular dysfunction occurs despite standard catecholamine therapy, milrinone can provide additional and effective inotropic support.

Milrinone has been shown to increase CI and improve hemodynamics in a variety of cardiac surgical and CHF patients. Fenec [14] studied 99 adult patients after elective cardiac operation who had a low CO (CI < 2.5 L · min⁻¹ · m⁻²) with a pulmonary artery occlusion pressure of 8 mm Hg or higher. In this study, patients received a loading dose of milrinone (50 μg/kg over a 10-minute period) followed by a continuous infusion of one of three dosages—0.375, 0.5, or 0.75 μg · kg⁻¹ · min⁻¹ (low-, middle-, and high-dose groups, respectively)—administered for a minimum of 12 hours. Patients were sequentially allocated to each dosage group. Hemodynamic measurements were made prior to therapy and up to 12 hours after the start of milrinone therapy. Milrinone treatment resulted in a rapid, well-sustained, and highly significant increase in CI in all three dosage groups and a similar reduction in pulmonary artery occlusion pressure in all groups. Significant reductions were also observed in systemic vascular resistance and pulmonary vascular resistance (PVR), although changes in the latter were less predictive and more dose dependent. Further analysis revealed that low CI (1.59 L · min⁻¹ · m⁻²), high resting PVR (>200 dynes s cm⁻⁵), and low mean arterial pressure (64 mm Hg) prior to treatment were predictors of a good therapeutic response to milrinone [15].

Another placebo-controlled, double-blind study [16] demonstrated the benefits of milrinone in facilitating weaning of high-risk patients from CPB. Patients were randomized to receive either intravenous milrinone (50–μg/kg loading dose over 20 minutes followed by 0.5–μg · kg⁻¹ · min⁻¹ infusion) or placebo 15 minutes before withdrawal from CPB. Of the 30 patients who completed the study, bypass support was withdrawn successfully in all 15 patients randomized to receive milrinone but in only 5 of the 15 patients randomized to receive placebo. The remaining 10 patients in the placebo group who were unable to be separated from CPB had milrinone administered in an open-label phase. After receiving milrinone treatment, these remaining patients were successfully withdrawn from CPB.

Using both standard hemodynamic measures and echocardiography, Kikura and coworkers [17] studied the effects of milrinone in cardiac surgical patients immediately after separation from CPB. The results of this study indicated that milrinone improved LV function and he-
modynamics in patients who were undergoing treatment with catecholamines, vasodilators, or both under constant loading conditions maintained by volume reinfusion from the CPB reservoir. All milrinone dosing regimens (50–μg/kg bolus only, 50–μg/kg bolus plus 0.5–μg · kg⁻¹ · min⁻¹ infusion, and 75–μg/kg bolus plus 0.75–μg · kg⁻¹ · min⁻¹ infusion) significantly increased CI, stroke volume index, and velocity of circumferential fiber shortening. After 5 and 10 minutes, these values were significantly higher in the milrinone groups than in the control group (Figs 1, 2). The increase in velocity of circumferential fiber shortening indicated a positive inotropic effect of milrinone in cardiac surgical patients.

This study confirmed the dose–response relationship previously demonstrated by Butterworth and colleagues [18]. These investigators found that in cardiac surgical patients, bolus doses of milrinone, 50 to 75 μg/kg, produce significantly larger increases in CI than a 25–μg/kg bolus dose immediately after separation from CPB. However, a dose of 75 μg/kg did not produce a significantly larger increase in CI than did a 50–μg/kg dose. This study indicates that a 50–μg/kg loading dose is more potent than a 25–μg/kg dose and as potent as a 75–μg/kg dose. Although the recommended loading dose for treatment of deteriorating ventricular function after separation from CPB is 50 μg/kg [18], a loading dose of 20 μg/kg followed by an infusion of 0.5 μg · kg⁻¹ · min⁻¹ provides hemodynamic support similar to that observed with a loading dose of 40 μg/kg followed by an infusion of 0.5 μg · kg⁻¹ · min⁻¹ in elective coronary artery surgical procedures [19].

Vascular Effects
Milrinone has a potent ability to reverse vasospasm in arterial grafts [20]. The pathophysiology of vasospasm in arterial grafts is complex and includes multiple factors, of which platelet activation and release of thromboxane A₂ may be the most important [21]. Reversing vasospasm is often challenging. Several studies [21, 22] have demonstrated the vasodilative effect of milrinone in internal mammary artery (IMA) rings harvested from patients undergoing coronary artery bypass grafting with IMA as bypass conduits. Salmenpera and Levy [20] reported the ability of PDE inhibitors in vitro to reverse the constriction of human IMA rings induced by a thromboxane A₂ analogue (U46619). Milrinone, amrinone, and enoximone each produced complete inhibition of the contractile response induced by U46619 in the IMA rings (Fig 3). Milrinone was the most potent inhibitor (0.3 ± 0.1 × 10⁻⁵ mol/L). The potency ratios of milrinone obtained for IMA vasodilation are compatible with the recommended clinical infusion doses [21]. In addition, these potency ratios are within range of the ratio of plasma milrinone concentrations that lead to a 50% increase in CI or ventricular

Fig 1. Changes in cardiac index (CI) after intravenous administration of milrinone (MIL) after separation from cardiopulmonary bypass. Data are shown as the mean ± the standard deviation. Cardiac index increased significantly from baseline (time 0) to 5 and 10 minutes in all milrinone-treated groups and was significantly higher at 5 and 10 minutes than in the control group. No significant changes were observed in the control group. (* = p < 0.05 versus baseline; † = p < 0.05 versus control group.) (Reprinted from Kikura M, Levy JH, Michelsen LO, et al. The effect of milrinone on hemodynamics and left ventricular function after emergence from cardiopulmonary bypass. Anesth Analg 1995;81:783–92 [17], with permission.)

Fig 2. Changes in velocity of circumferential fiber shortening corrected for heart rate (Vcfc) after intravenous administration of milrinone (MIL) after separation from cardiopulmonary bypass. Data are shown as the mean ± the standard deviation. The velocity of circumferential fiber shortening increased significantly from baseline (time 0) to 5 and 10 minutes in all milrinone-treated groups and was significantly higher than 5 and 10 minutes than in the control group. No significant changes were observed in the control group. (* = p < 0.05 versus baseline; † = p < 0.05 versus control group.) (Reprinted from Kikura M, Levy JH, Michelsen LO, et al. The effect of milrinone on hemodynamics and left ventricular function after emergence from cardiopulmonary bypass. Anesth Analg 1995;81:783–92 [17], with permission.)
contractility in patients with CHF and in cardiac surgical patients [4].

Vasospasm of arterial grafts represents an unpredictable complication of coronary artery surgical procedures and can compromise myocardial revascularization. Treatment is typically based on empirical therapy with nitroglycerin. However, tolerance of nitroglycerin can develop. Also, nitrovasodilators function by way of cGMP and require an intact endothelium. In contrast, the mechanism of vasorelaxation for PDE III inhibitors, such as milrinone, is mediated by an increase in cAMP. Milrinone has little effect on cGMP, and it has been demonstrated that denudation of endothelium does not affect milrinone-induced relaxation [21]. This suggests that milrinone could potentially be used to prevent and treat IMA spasm, which contributes to early myocardial ischemia and may even cause death in patients undergoing coronary artery bypass grafting [23].

Huraux and coworkers [22] investigated the effect of different vasodilators that act through separate pathways on segments of human IMA precontracted with norepinephrine, potassium chloride, or the thromboxane A2 analogue U46619. Milrinone, nitroglycerin, papaverine hydrochloride, prostaglandin E1, and isradipine, a dihydropyridine, were added to precontracted isolated IMA segments. The vasodilators induced 90% to 100% relaxation of the constricted vascular rings with the exception of prostaglandin E1, which produced only 73% relaxation of U46619-treated IMA segments at maximal concentrations. Another study [24] reported findings that suggest that milrinone and nitroglycerin may act synergistically, producing greater than expected results when combined.

Antiinflammatory Effects

Mollhoff and colleagues [25] evaluated the effects of milrinone on splanchnic oxygenation, systemic inflammation, and the acute-phase response in 22 adult patients undergoing coronary artery bypass grafting. Milrinone was administered as a bolus of 30 μg/kg over a period of 10 minutes followed by a continuous infusion of either milrinone, 0.5 μg · kg⁻¹ · min⁻¹, or saline solution. The following variables were recorded: hemodynamics; systemic oxygen delivery and uptake; arterial, mixed venous, and hepatic venous oxygen saturations; intramusosal pH; and mixed and hepatic venous plasma concentrations of endotoxin, interleukin-6, serum amyloid A, and C-reactive protein. Although milrinone did not prevent gastrointestinal acidosis, as measured by intramusosal pH, its perioperative administration resulted in significantly higher intramusosal pH levels compared with control. In addition, venous and hepatic venous endotoxin levels and interleukin-6 concentrations were reduced significantly in the milrinone group, and serum amyloid A values were attenuated in the milrinone group 24 hours after operation. No significant differences were observed in routinely measured oxygen transport-derived variables. The authors suggested that perioperative administration of low-dose milrinone may have anti-inflammatory properties and may improve splanchnic perfusion in otherwise healthy patients undergoing routine coronary artery bypass grafting. Milrinone may also provide an additional beneficial effect by dilating the splanchnic vasculature, even in the presence of potent vasopressors [26].

Use in Children

Chang and associates [27] administered milrinone, 50 μg/kg, over 15 minutes to 10 neonates after a cardiac surgical procedure and observed an average increase in CI of 42% and average decreases in systemic vascular resistance and PVR of 37% and 27%, respectively. These changes were associated with decreases in right and left atrial pressures. Bailey and colleagues [28] characterized the pharmacodynamics and pharmacokinetics of milrinone in 20 children after they underwent repair of congenital cardiac defects. A loading dose of 50 μg/kg given over a period of 5 minutes resulted in a mean decrease in mean arterial pressure of 12% and a mean increase in CI of 18% at a mean peak plasma concentration of 235 ng/mL.

Milrinone has a larger volume of distribution and a higher elimination clearance in infants and children than in adults. A loading dose of 50 μg/kg achieves therapeutic plasma concentrations in infants and children, but the plasma concentration may become temporarily subtherapeutic in the first 30 minutes of administration unless a supplementary dose is given in addition to the maintenance infusion of 0.5 μg · kg⁻¹ · min⁻¹. Simulations using
the derived pharmacokinetic indicators suggest that an appropriate concentration can be achieved by administering a loading dose of 50 μg/kg followed by an infusion of approximately 3 μg·kg\(^{-1}\)·min\(^{-1}\) for 30 minutes and a maintenance infusion [28].

**Use in Orthotopic Heart Transplantation**

Givertz and coworkers [29] reported the use of milrinone to test pulmonary vascular reactivity in patients with severe CHF before orthotopic heart transplantation. In 27 patients with functional class III or IV heart failure with a PVR of 200 dyne s cm\(^{-5}\) or higher, a single milrinone dose (50 μg/kg) infused over 1 minute decreased PVR in all patients. The effect was maximal 5 to 10 minutes after the dose and persisted for at least 20 minutes. The mean decrease in PVR at 5 minutes (31% ± 4%) was associated with a 42% ± 4% increase in CO and decreases of 12% ± 4% and 16% ± 5% in mean pulmonary artery pressure and pulmonary artery occlusion pressure, respectively. No change in transpulmonary pressure gradient was observed. Milrinone had no effect on heart rate or arterial pressure. The magnitude of the decrease in PVR correlated inversely with the milrinone-induced increase in CO. The authors suggested that an intravenous milrinone dose can be used to test for the reversibility of pulmonary hypertension in patients with CHF undergoing evaluation for orthotopic heart transplantation, although most centers prefer use of shorter-acting agents. Pamboukian and colleagues [30] also reported the efficacy of milrinone in lowering PVR in patients undergoing orthotopic heart transplantation.

Sherry and Locke [31] used milrinone as a pharmacologic bridge to orthotopic heart transplantation by improving decompensated CHF in patients in whom the response to β agonists was inadequate. The condition of 1 patient with β agonist–resistant CHF and balloon counterpulsation was stabilized with milrinone for 21 days and subsequently was maintained with medical therapy until heart transplantation 3 months later. Stabilization of another 9 patients with severe decompensated CHF was accomplished for between 11 and 51 days with milrinone. Seven of the patients received donor hearts, and 2 patients died before suitable organs could be found. All patients in the study demonstrated clinical improvement within 48 hours after treatment with milrinone was initiated.

**Adverse Effects**

Rapid milrinone administration produces high peak plasma levels, decreasing systemic vascular resistance and venous return and causing hypotension, especially in hypovolemic patients. Therefore, slower administration of milrinone over 10 minutes is recommended. Decreases in preload may require substantial volume loading. In addition, concomitant administration of α-adrenergic agents such as phenylephrine, norepinephrine, or dopamine hydrochloride attenuates the potential for vasodilation. When hypotension is refractory to norepinephrine, low-dose vasopressin therapy can be useful [32, 33].

Like all positive inotropic agents, milrinone has possible proarrhythmic effects. Oral milrinone did not receive approval from the Food and Drug Administration because of increased mortality compared with placebo and increased incidence of syncope, possibly attributable to proarrhythmic effects [34]. The major electrophysiologic effect of intravenously administered milrinone is enhanced atrioventricular node conduction [35]. However, increased ventricular ectopy can occur with short-term intravenous therapy [36].

Amrinone, the first PDE III inhibitor, that is now called inamrinone has been associated with thrombocytopenia during therapy [36–39]. The mechanism of inamrinone-induced thrombocytopenia is thought to be a nonimmune-mediated toxic effect of inamrinone or its metabolite (N-acetyl amrinone) on megakaryocytes or platelets, resulting in decreased survival time of the platelet [38]. In platelets, cAMP generated from adenosine triphosphate by adenyl cyclase serves as an intracellular messenger to inhibit the platelet activation sequence at numerous steps [40]. Phosphodiesterase inhibitors can affect platelet aggregation in vitro [41]. However, compared with amrinone, milrinone does not seem to have an adverse effect on platelets. A study by Kikura and associates [42] demonstrated that short-term milrinone administration did not cause significant changes in platelet number or function in patients undergoing cardiac operations requiring CPB, beyond the usual adverse effects of a cardiac surgical procedure and CPB.

**Comment**

Milrinone is a selective inhibitor of the cAMP–specific phosphodiesterase III isoenzyme in myocardium and vascular smooth muscle. By increasing cAMP concentrations in both myocardium and vascular smooth muscle, milrinone causes an increase in CO through combined positive inotropic and vasodilative effects. Administration of milrinone is typically associated with a decrease in systemic blood pressure and cardiac filling pressures. This drug has been used effectively during separation from CPB and for the treatment of low CO syndrome after cardiac operations. Its pharmacokinetics are more prolonged than those of the catecholamines commonly used for inotropic support after cardiac surgical procedures. Administration requires both a loading dose and a continuous infusion.

Milrinone may be particularly efficacious in patients who are at risk for β-receptor down-regulation, such as those with CHF prior to operation. Milrinone may prevent or attenuate vasospasm of arterial conduits. It has been used effectively in the treatment of right ventricular failure, particularly after orthotopic heart transplantation.

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