Inhaled Milrinone After Left Ventricular Assist Device Implantation

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ABSTRACT

Background: Proven strategies to reduce right ventricular (RV) dysfunction after continuous-flow left ventricular assist device (CF-LVAD) implantation are lacking. We sought to evaluate the tolerability, feasibility, efficacy, and pharmacokinetics of inhaled milrinone (iMil) delivery after CF-LVAD implantation.
Methods and Results: We prospectively evaluated fixed-dose nebulized iMil delivered into a ventilator circuit for 24 hours in 10 postoperative CF-LVAD (Heartmate-II) patients. Tolerability (arrhythmias, hypotension, and hypersensitivity reaction), efficacy (hemodynamics), pharmacokinetics (plasma milrinone levels), and cost data were collected.Mean age was 56 ± 9 years, 90% were male, and mean INTERMACS profile was 2.5 ± 0.8. No new atrial arrhythmia events occurred, although 3 (30%) ventricular tachycardia (1 nonsustained, 2 sustained) events occurred. Sustained hypotension, drug hypersensitivity, death, or need for right ventricular assist device were not observed. Invasive mean pulmonary arterial pressure from baseline to during iMil therapy was improved ($P = .017$). Mean plasma milrinone levels (ng/mL) at baseline, and 1, 4, 8, 12, and 24 hours were 74.2 ± 35.4, 111.3 ± 70.9, 135.9 ± 41.5, 205.0 ± 86.7, 176.8 ± 61.3 187.6 ± 105.5, respectively. Reduced institutional cost was observed when iMil was compared with nitric oxide therapy over 24 hours ($165.29 vs $1,944.00, respectively).
Conclusions: iMil delivery after CF-LVAD implantation was well tolerated, feasible, and demonstrated favorable hemodynamic, pharmacokinetic, and cost profiles. iMil therapy warrants further study in larger clinical trials. (*J Cardiac Fail 2015;21:792−797*)
Key Words: Phosphodiesterase inhibitor, nebulization, right ventricular dysfunction, left ventricular assist device.

The 6th annual report of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) describes right ventricular (RV) dysfunction occurring in a significant portion of patients who undergo continuous-flow left ventricular assist device (CF-LVAD) implantation.[1] Studies demonstrate that RV dysfunction after CF-LVAD implantation results in an increase in perioperative morbidity and mortality.[2] Patients requiring early right ventricular assist device (RVAD) support after LVAD have increased mortality.[1] Besides increased mortality, RV dysfunction has been associated with prolonged intensive care unit (ICU) and hospital length of stay and increased incidence of renal dysfunction after implant.[2−4] Optimizing RV function after CF-LVAD implantation may decrease morbidity and mortality and improve patient outcomes. Current strategies to minimize the occurrence of RV dysfunction include inhaled nitric oxide and inhaled

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epoprostenol; however, these options are expensive, are cumbersome to administer and may lead to rebound pulmonary hypertension. Additionally, conflicting data supporting the efficacy of these therapeutic strategies has been reported.[5]

Milrinone, a phosphodiesterase-III inhibitor, increases the intracellular concentration of cyclic adenosine monophosphate (cAMP) in vascular smooth muscle as well as cardiac myocytes. Increased intracellular cAMP results in pulmonary and systemic vasodilatation, increased inotropy and increased lusitropy.[6] Intravenous milrinone therapy is limited by systemic hypotension and lack of pulmonary vasculature selectivity, thus limiting its clinical utility and effectiveness.[7]

Inhaled milrinone, in contrast to systemic administration, may be delivered directly to the airways, resulting in maximal local drug effect (pulmonary arterial vasodilation) while minimizing systemic side effects. Although human studies with the use of inhaled milrinone have not been reported in a CF-LVAD population, studies have been performed in other populations, demonstrating improved pulmonary hemodynamics and RV functional parameters.[8−12] Furthermore, these studies did not report increased risk of hypotension, arrhythmia, systemic drug reaction, or death due to the administration of inhaled milrinone.

We sought to primarily evaluate the feasibility and safety of inhaled milrinone, and secondarily evaluate the pharmacokinetics, efficacy, and cost profile of inhaled milrinone in patients undergoing CF-LVAD implantation. We propose that the administration of nebulized inhaled milrinone directly into the ventilator circuit of patients will be a feasible, well tolerated, and effective alternative to conventional therapies.

Methods

Patients fulfilling standard criteria for CF-LVAD placement at the University of Nebraska Medical Center were recruited for enrollment from April 2012 to June 2013. The protocol was approved by the University of Nebraska Institutional Review Board. Patients deemed to be appropriate for bridge to transplant or destination therapy indications consented before CF-LVAD implantation to receive postoperative inhaled milrinone. Ten consecutive patients consented and received inhaled milrinone therapy. Data were collected prospectively. Exclusion criteria included pregnant or breastfeeding patients and documented allergy to milrinone. Patients were compared with institutional and national database CF-LVAD control subjects. All institutional controls underwent inhaled nitric oxide therapy and intravenous (IV) administration of milrinone. Patients enrolled in this study received inhaled milrinone in place of inhaled nitric oxide (40 ppm) and IV milrinone. All patients were converted to IV milrinone, if clinically indicated, after study protocol was completed.

Study End Point Determination

The primary end point was safety, which included documentation of 1) new atrial arrhythmias lasting >30 seconds or resulting in hemodynamic instability (mean arterial pressure [MAP] <60 mm Hg or requiring medical intervention), 2) sustained ventricular tachycardia (VT) lasting >30 seconds, not related to an LVAD suction event or any ventricular arrhythmia resulting in hemodynamic instability (sustained hypotension with MAP <60 mm Hg not related to secondary causes such as acute blood loss or tamponade), 3) hypersensitivity reaction to milrinone leading to systemic hypotension (MAP <60 mm Hg or requiring medical intervention), bronchospasm, or rash, and 4) death by 30 days.

Secondary end points were designed to assess the efficacy, cost-effectiveness, and pharmacokinetic profile of inhaled milrinone therapy. Efficacy end points included hospital and ICU lengths of stay, days on inotropes, mortality at 30 days, and changes in RV stroke work index (RSVWI)[13] and right heart catheterization and echocardiographic parameters from baseline values. Right heart catheterization was performed during the hospitalization before LVAD implantation and included the following parameters: right atrial pressure (RAP), mean pulmonary arterial pressure (mPAP), pulmonary arterial systolic pressure (PASP), cardiac index (CI), and cardiac output (CO). Echocardiographic data was collected retrospectively from echocardiograms closest to the LVAD implantation date (studies performed >1 month before surgery were not included) and prospectively obtained within 72 hours after LVAD implantation. Echocardiographic parameters included: LV end-diastolic volume (LVEDV), LV end-diastolic dimension (LVEDD), cardiac output (CO), PASP, qualitative RV function, and tricuspid annular plane systolic excursion (TAPSE).

Blood samples to determine plasma milrinone levels were obtained at baseline and 1, 4, 8, 12, and 24 hours after initiation of inhaled milrinone. Plasma milrinone levels were determined with the use of an ultraviolet high-performance liquid chromatography (HPLC) method.[14]

Equipment and medication costs of inhaled milrinone delivery were compared with inhaled nitric oxide therapy on a per-patient basis calculated over the study duration (24 hours). All cost data were calculated based on institutional 2012 prices.

Characterization of Inhaled Milrinone

Inhaled milrinone validation studies were performed before study initiation to characterize inhaled milrinone aerosol particle size, evaluate nebulization degradation profile, and quantify drug delivery with the use of a vibrating mesh nebulizer connected to a mechanical ventilator circuit. Mass spectrometry analysis of inhaled milrinone samples did not identify new drug formation or degradation products. A pharmaceutical-grade impactor was used to determine median aerodynamic particle size, and HPLC was used to determine the amount of milrinone collected at the distal end of the experimental endotracheal tube.[15] Based on this analysis, we prepared a solution of milrinone diluted in 0.9% saline solution to a final concentration of 0.5 mg/mL to be delivered via continuous infusion by means of an Alaris infusion pump set at a fixed rate of 12 mL/h connected to an Aerogen Solo (Aerogen, Galway, Ireland) vibrating mesh nebulizer and Aerogen Pro-X nebulizer control unit. The nebulizer was connected to a mechanical ventilator (Servo-I; Maquet, Wayne, New Jersey) with a dual heated wire ventilator circuit (Teleflex Hudson RCI, Research Triangle Park, North Carolina) proximal to the heated humidifier (Teleflex Hudson Neptune). Despite continuous nebulization, delivery of the aerosolized drug product occurred in an ''intermittent-continuous'' fashion based on the mechanical ventilator