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Continuous Intravenous Milrinone Therapy in Pediatric Outpatients

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ABSTRACT

Milrinone is a phosphodiesterase 3 inhibitor with both positive inotropic and vasodilator properties. Administered as a continuous infusion, milrinone is indicated for the short-term treatment of patients with acute decompensated heart failure. Despite limited data supporting long-term milrinone therapy in adults with congestive heart failure, children managed as outpatients may benefit from continuous milrinone as a treatment for cardiac dysfunction, as a destination therapy for cardiac transplant, or as palliative therapy for cardiomyopathy. The aim of this article is to review the medical literature and describe a home infusion company's experience with pediatric outpatient milrinone therapy.

Key words: heart failure, intravenous, milrinone, outpatient, pediatric

Milrinone lactate is a cardiotonic agent that has both inotropic and vasodilating effects. The selective phosphodiesterase inhibitory activity of milrinone increases intracellular cyclic adenosine monophosphate levels in myocardial and vascular smooth muscle cells. The result is an increase in intracellular calcium, which enhances myocardial contractility with minimal chronotropic effect. Physiologically, milrinone contributes to an increase in cardiac output but decreases pulmonary capillary wedge pressures and vascular resistance. Administered as a continuous infusion, the reported adverse effects of milrinone include ventricular arrhythmias, hypotension, and headache.

The primary indication for milrinone is short-term management of acutely decompensated congestive heart failure, but it has also been used for postoperative cardiac patients with heart failure. Generally, inotropic infusions are reserved for inpatient use, but outpatient treatment was reported initially with dopamine and dobutamine.[1–3] Use of milrinone has become more prevalent for the treatment of outpatient pediatric heart failure patients. Outpatient management of children with heart failure improves the patient and family experience and decreases costs associated with prolonged hospitalization. Continuous milrinone therapy in selected pediatric outpatients in a palliative care setting, or as a destination therapy for heart transplant, can be performed safely and improve quality of life.

REVIEW OF THE LITERATURE

Home milrinone therapy in adults was first reported more than 2 decades ago.[4] Early reports suggested a benefit of home intravenous (IV) inotropic therapy to support adults awaiting heart transplant.[5,6] A recent review has suggested that, with the exception of digoxin, IV inotropic agents should be reserved for inpatient treatment of adults with acute decompensated congestive heart failure in association with low cardiac output that impacts organ perfusion.[7] An additional review[8] identified increased mortality in adults treated with inotropes for advanced heart failure, but others have described potential benefits associated with palliative inotropic therapy.[9]

Home inotropic therapy in children awaiting heart transplantation was first reported in 2006 in a cohort of 7 patients.[10] Four of the patients had congenital heart disease and the other 3 had either ischemic or idiopathic dilated cardiomyopathy. The mean age was 14.5 ± 3.7 years,

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and 6 of the patients received milrinone alone or in combination with dopamine. Mean duration of therapy for all 7 patients was 198 days (range 27–588). Pertinent findings included an improved estimated ejection fraction and a decrease in emergency department visits and hospitalization admissions while on therapy. Six of the patients successfully underwent heart transplantation. One patient without an implantable cardiac defibrillator (ICD) died at home from a presumed arrhythmia. There were 5 catheter-related complications in 2 patients, and only 1 of these was attributable to a central line-associated bloodstream infection (CLABSI).

Outpatient milrinone therapy has also been used for palliative care of end-stage congestive heart failure. Berg et al[11] reported their experience with 14 pediatric patients (median age 14.5 years), 8 of whom received inotropic support as palliative care. Two of these patients had muscular dystrophy, 1 had dilated cardiomyopathy, 1 had congenital heart disease, and the remaining 4 palliative care patients had graft failure from previous heart transplants. Five of the remaining 6 patients received milrinone as a bridge to transplant, with 5 successful transplants and the sixth patient awaiting transplant at the time of publication. None of the patients had an ICD. Median duration of inotropic therapy was 68 days (range 14–476), and all patients had central venous catheters (CVCs) monitored by weekly nursing visits. Four CLABSIs resulted in catheter changes. Reported benefits from this study included decreased family stress with the child at home with parents and siblings, and a cost savings of more than $600 dollars a day in comparison with hospitalization.

Another report described 5 palliative care and 10 heart transplant–listed patients treated for advanced heart failure with a median age of 5 years (range 2–17).[12] Mean duration of outpatient milrinone therapy was 36.3 $\pm$ 30.1 days. Nine of the heart transplant listed patients were successfully transplanted. There were 4 catheter-related complications during outpatient therapy. The authors concluded that in a carefully selected pediatric population, outpatient milrinone therapy is safe and efficacious.

The largest series of pediatric patients to receive IV inotropic therapy as a bridge to cardiac transplant was reported by Birnbaum et al.[13] Over a period of 13 years, 106 pediatric patients awaiting transplant were discharged home on inotropic therapy and 91% were treated with milrinone. The mean age was 10.1 $\pm$ 6.4 years. A diagnosis of congenital/structural heart disease accounted for 47%, with the remaining patients having nonstructural causes, including but not limited to dilated, restricted, and hypertrophic cardiomyopathies, arrhythmias, and myocarditis. Infusions were administered through CVCs. Either an implanted or external defibrillator was present in 26% of patients, but only 2% of patients had a clinically significant arrhythmia while on therapy. The median duration of therapy for patients awaiting transplantation was 47 days (range 4–323). Eleven different catheter malfunctions occurred in 6 different patients, with CLABSI identified in 5 patients. Ninety patients went on to successful transplant, 1 was awaiting transplant at the time of publication, 9 were weaned off inotropic support, and 6 patients died, but only 1 from sudden cardiac death.

Since 2008, Pediatric Home Service (PHS) in Roseville, MN, has provided milrinone for home infusion. The following describes our experience with outpatients with heart failure receiving parenteral milrinone.

METHOD

Design and Sample

This study used a retrospective chart review to identify patients referred to a pediatric home infusion company (PHS; Roseville, MN) for continuous outpatient milrinone therapy. Twelve patients received continuous milrinone therapy as outpatients between 2008 and 2015 inclusive. All patients were tolerating IV milrinone therapy as inpatients before discharge on home infusions. This study was approved by the Children's Hospital and Clinics of Minnesota institutional review board.

Role of Home Infusion Nurses

Initially the home infusion nurse processed the referral for home-based inotropic therapy and verified that the physician orders included frequency of home visits, weight and vital sign monitoring, acceptable parameter limits, and the maximum time the patient could be off the infusion in the event of a catheter malfunction. If possible, a recommendation was made that patients come home with a double-lumen CVC. In addition, the infusion nurse evaluated the need for medical devices such as a defibrillator, blood pressure monitor, scale, IV pump, back-up pump, and pump battery/power source. Drug dosing, flushing protocols, laboratory draws, and procedure for treatment of catheter occlusion typically mirrored the protocols of the hospital from which the patient was discharged. In-home caregivers were identified and received instruction on the medical devices, catheter assessment, medication bag changes, patient assessment, and monitoring and recording of vital signs. Infusion pump program changes were always double-checked by a second nurse or pharmacist and documented in the patient's electronic medical record. Frequent visits were often needed until the caregiver was fully trained and comfortable with the skills needed to provide therapy. Thereafter, an infusion nurse visited 1 to 2 times per week for patient assessment and CVC dressing changes.

Drug Preparation

Pharmacy prepared milrinone in 5% dextrose to the same concentration the patient received as an inpatient. The IV rate also remained the same as prescribed as an inpatient and ranged from 0.3 mcg/kg/min to 1 mcg/kg/min with a median of 0.5 mcg/kg/min for study patients. Generally, IV

TABLE 1

Patient Demographics

Patient	Diagnosis	Age (Years)	Indication	Total Outpatient Days	Number Readmissions During Therapy	Outcome
1	CHD	5	Pre- and posttransplant	173	0	Transplant then weaned off
2	CHD	11	Pre- and posttransplant	150	4	Transplant then weaned off
3	CHD	8	Postsurgery	29	0	Weaned off
4	CMP	6	Postsurgery	22	0	Weaned off
5	CMP	22	Posttransplant	25	1	Weaned off
6	CMP	1	Pretransplant	31	1	Transplant
7	CHD	2	Pretransplant	73	1	Death
8	CHD	2	Pretransplant	389	15	Transplant
9	CMP	15	Presurgery	15	0	Weaned off
10	CMP	15	Palliative	54	0	Death
11	CMP	11	Pretransplant	33	1	Transplant
12	CHD	4	Palliative	N/A	0	On Therapy

Abbreviations: CHD, congenital heart disease; CMP, cardiomyopathy.

TABLE 2

Treatment and Complications per Patient

Intervention	Number of Patients
Readmission during therapy[a]	6/12
Defibrillator device	5/12
Dopamine	1/12
Nursing	
SNV	7/12
HCN	3/12
Both SNV/HCN	2/12
Catheter type	
PICC single lumen	1/12
PICC double lumen	9/12
Tunneled single lumen	1/12
Tunneled double lumen	1/12
Catheter complications	
Occlusion needing treatment	2/12
Leak, disconnect, or crack	2/12
Catheter inadvertently pulled/ dislodged	1/12
Skin issues	2/12
Pump malfunctions	1/12
CLABSI	0/12

[a]Excluding scheduled admission or for available donor heart transplant.
Abbreviations: HCN, home care nursing (extended hour); SNV, skilled nurse visit; PICC, peripherally inserted central catheter; CLABSI, central line-associated bloodstream infection.

bags were changed every 2 to 3 days with premixed backup bags available in the patient's home.

RESULTS

This study identified 12 patients referred for outpatient milrinone therapy (Table 1). The mean age was 8.5 years, and 7 of 12 cases were males. The most common indication was treatment of heart failure before heart transplant. Three patients required outpatient treatment after heart transplant and were successfully weaned off therapy. Two other patients were treated with milrinone for cardiac dysfunction, 1 after cardiac transplantation and another after surgical repair of congenital heart disease. One patient received 15 days of milrinone before successful pericardiectomy for constrictive cardiomyopathy. Palliative care was limited to 2 patients: 1 for treatment of cardiomyopathy associated with Duchenne muscular dystrophy and the other for progressive heart failure associated with complex congenital heart disease. The median duration for all outpatient treatment, excluding patient number 12 who was still on palliative therapy, was 33 days. With the exception of 1 patient, all readmissions occurred in patients awaiting heart transplant.

Additional therapies and complications were also identified in this study (Table 2). Fifty percent of the patients required hospital readmission while they were on therapy. An automated external defibrillator, or a wearable cardiac defibrillator, initially was prescribed for 5 of the 12 patients; however, 1 wearable cardiac defibrillator was discontinued because of device malfunction. One patient was on dopamine in addition to milrinone. All patients received in-home nursing care. Skilled nursing visits were more common than

extended-hour home care nursing. Most infusions were provided via a peripherally inserted central catheter (PICC), and 3 patients with a PICC required 1 or more catheter replacements. A catheter-related complication, including occlusion, leakage, disconnection, dislodgement, or skin issues, occurred in 41.7% of the patients. There was 1 infusion pump malfunction, which required use of the back-up pump. Some providers alternate using 2 pumps with medication bag changes to ensure that both pumps are operational. No outpatient CLABSIs were confirmed in our study population.

DISCUSSION

In our study, 5 of 6 patients (83%) listed for heart transplant were transplanted successfully. One patient died awaiting transplant. Reports from other studies[10,13] cite transplantation success rates of 85% and 86%, respectively. Our study population had only 2 cases referred for palliative care, which differs from previous reports in which 33.3%[12] or 57%[11] of patients received palliative milrinone infusions. A previously unreported finding in our study was the use of milrinone in the outpatient setting for 4 patients with postsurgical cardiac dysfunction. Three of these patients were treated after heart transplantation and 1 after repair of congenital heart disease. All 4 of these patients successfully weaned off therapy.

The median outpatient treatment was 33 days (excluding patient 12) in our study, which is comparable with another mixed patient population with a reported mean of 36 days.[12] Wait times for pediatric heart transplant are quite variable, but in 2009, 55.9% of pediatric patients received a transplant within 12 months of being listed.[14] Consequently, duration of outpatient therapy may be prolonged for some patients. A mean of 170 outpatient therapy days for the 4 patients bridged to transplant in our study is comparable with 198 days reported in another study.[10]

Adults with heart failure are reported to have an increased risk for sudden death associated with arrhythmias. One recommendation was for insertion of implantable cardiac defibrillators for all pediatric transplant candidates managed as outpatients on inotropic therapy.[10] In 2005, sudden death was reported to be uncommon in children awaiting heart transplant, with an incidence of 1.3%.[15] The most recent study of outpatient children awaiting heart transplant identified that 26% had a prescribed defibrillator device in the home.[13] In our 6 pretransplant cases, 5 patients had a defibrillation device in the home, and to our knowledge none of the patients required cardioversion while on outpatient therapy.

Similar to our study, PICCs predominate as the catheter of choice for inotropic infusion in children, with reports of 53% and 100% in other studies,[10,13] respectively. Catheter malfunction, including occlusion, leakage, disconnection, or dislodgement, occurred in 5 of our patients (41.6%). This is in contrast to 28.6% and 6% previously reported.[13,10] The use of a double-lumen catheter is recommended. In the event of a catheter occlusion, the infusion can be moved to the second lumen with little or no interruption of therapy and could potentially avoid rehospitalization. The use of a back-up pump in the home is essential to prevent interruption in therapy caused by pump malfunction. Also, consider alternating 2 pumps with bag changes to ensure that both pumps function properly.

Hospital readmission is a common occurrence in this high-risk population, and in the largest study occurred at least once in 50% of patients on home inotropic therapy.[13] Worsening heart failure accounted for the majority of readmissions, whereas infections and catheter malfunctions were the second and third most common reasons, respectively.[13] In our study, 50% of our patients were readmitted at least once.

Generally, an infusion nurse performs a home visit once a week while outpatients are being treated with milrinone. A PHS cost analysis for a week of milrinone therapy, including a single nurse visit, approximates $775. A 2009 report found a pediatric hospital bed costs $2300 per day or $16 100 a week.[16] In lieu of hospitalization, outpatient milrinone therapy conceivably can reduce costs by greater than $15 000 a week.

CONCLUSIONS

Our experience with milrinone therapy is comparable with reports published previously. Outpatient therapy allows patients to thrive at home with as normal a routine as possible. Decreasing hospital days minimizes risk for nosocomial infections and decreases costs. In a select pediatric patient population either listed for heart transplant, recovering from cardiac surgery/transplant, or in palliative care, outpatient milrinone therapy was safe with few complications.

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