ESC HEART FAILURE
ESC Heart Failure 2022; **9**: 4340–4343
Published online 29 July 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14092

SHORT COMMUNICATION

Oral milrinone for management of refractory right ventricular failure in patients with left ventricular assist devices

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Abstract

Aims We present a single-centre retrospective experience using oral milrinone in patients with a left ventricular assist device (LVAD) and concurrent refractory right ventricular failure.

Methods and results All patients implanted with LVAD between January 2013 and July 2021 from a high-volume advanced heart failure service were reviewed. Eight patients were initiated on oral milrinone during this period. Oral milrinone was started 1.5 [inter-quartile range (IQR) 1–2.3] years after LVAD implantation and continued for 1.2 (IQR 0.5–2.8) years. Therapeutic milrinone levels were achieved (232.2 ± 153.4 ng/mL) with 62.4 ± 18% of time within the therapeutic range. Two patients had adverse events (non-sustained ventricular tachycardia and ventricular fibrillation effectively treated by internal cardioverter defibrillator) but did not require milrinone discontinuation. Four deaths occurred, one after transplant and three from disease progression determined to be unrelated to oral milrinone use. Three patients continue oral milrinone therapy in the community. There was no significant difference found after the initiation of oral milrinone on any of the physiological measures; however, there were trends in reduction of New York Heart Association class from 3.4 ± 0.5 to 3.0 ± 0.8 (P = 0.08), reduction of right atrial/wedge pressure from 0.9 ± 0.3 to 0.5 ± 0.2 (P = 0.08), and improvement of right ventricular stroke work index from 3.8 ± 2 to 5.8 ± 2.7 (P = 0.16).

Conclusions Oral milrinone appears safe for long-term use in the outpatient setting when combined with therapeutic monitoring in this complex medical cohort with limited management options. Further study is needed to ascertain whether this treatment is effective in reducing heart failure symptoms and admissions.

Keywords Oral milrinone; LVAD; Ventricular assist device; Inotropes

Received: 27 March 2022; Revised: 10 July 2022; Accepted: 18 July 2022
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Background

Right ventricular failure occurs in up to 50% of left ventricular assist device (LVAD) patients.[1] Management is complex involving adjustment of pump speed, optimization of fluid balance, use of inotropic agents such as milrinone to improve right ventricular function, and transplantation.

Milrinone is a phosphodiesterase III inhibitor used intravenously to optimize cardiac output, systemic and pulmonary pressures as a bridge to heart transplantation,[2] and to optimize ventricular function perioperatively.[3] In the UK, its use is reserved for inpatient therapy, although internationally, it has been delivered as an outpatient for some time.[4]

Oral milrinone provides a means of delivering inotropic support without the requirement for intravenous (IV) lines and pumps. IV milrinone formulation is taken orally four times a day (QDS) and has been shown to have an oral bioavailability of 92%.[5] Although there are historical data showing deleterious pro-arrhythmogenic effects with use of oral milrinone in heart failure,[6] contemporary pilot studies in

heart failure[7,8] and LVAD patients[9] have shown potential indications for use.

Aims

We looked to assess the use of oral milrinone in patients implanted with an LVAD to reduce symptoms secondary to refractory right ventricular impairment.

Methods

We determined this approach to be safe based on two principles. Firstly, although ventricular arrhythmias are associated with poorer long-term outcomes in patients with LVADs, they are generally well tolerated in the short term.[10] Secondly, we utilized our established therapeutic drug monitoring (TDM) system[9] for serum milrinone levels to limit time above the therapeutic range that could be associated with deleterious side effects.

This retrospective single-centre observational study reviewed all LVAD patients commenced on oral milrinone for refractory right ventricular failure in a high-volume advanced heart failure service between January 2013 and July 2021. All patients in this cohort were implanted with HeartWare Ventricular Assist System® (HVAD, Medtronic, Minnesota, USA). Patients initiated on oral milrinone were all consented for an off-licence use of medication. Decision on initiation was made clinically at our medical transplant multidisciplinary team after reviewing symptoms, and echo and invasive catheterization data that supported right ventricular failure after LVAD implantation as the dominant problem. In those patients stable on IV milrinone, the total daily dose administered was converted to the oral equivalent by multiplying by 1.1 (bioavailability is ~92%),[5] while those initiated on oral milrinone were started at a low dose of 0.22 μg/kg/min (equivalent to 0.2 μg/kg/min IV), with the total daily dose given in four doses and gradually titrating the dose upwards or downwards as necessary in the light of the measured level. A trough serum sample was taken 1–2 h prior to the next dose. Milrinone levels were measured using a high-performance liquid chromatography mass spectrometry with a target range 100–300 ng/mL. Milrinone was measured three times a week while in hospital, or more frequently by clinical request, with results available within 4 h. While in the community, milrinone was measured every 2–3 months and during clinic appointments when stable, or more frequently if there was a change in clinical condition, for example, renal function.

The Rosendaal method is most used to report time in therapeutic range (TTR) in clinical trials for warfarin anticoagulation, utilizing linear interpolation to estimate time a patient remains within a therapeutic international normalized ratio range.[11] It accounts for time elapsed since the last test, thereby avoiding the effect of varied test frequency. The milrinone TTR was calculated using this Rosendaal linear interpolation method. Each milrinone trough level is plotted at its time point, the difference between consecutive levels is assumed to be linear; using these linear estimates, TTR is calculated by summing the time during which the lines fall within the target milrinone range. However, the assumption of linear movement between milrinone values may pose a limitation as milrinone has a short half-life; larger studies are required to establish a quality benchmark, as with warfarin in the ambulatory setting. Out-of-range milrinone results may normalize more quickly following dose adjustment than as predicted by linear interpolation. Therefore, significant deviations from the therapeutic range will dramatically lower the overall TTR.

We assessed for adverse events including ventricular arrhythmia (symptomatic or lasting more than 30 s), vasodilation leading to hypotension requiring admission to hospital, or acute coronary syndrome occurring at any point after oral milrinone initiation.

We examined the physiological effects of oral milrinone through blood tests, echocardiography, and catheter studies. The pre-milrinone data were collected from results as close to the initiation of IV or oral milrinone. The post-milrinone data were collected at the first result after 3 months, with the exception of right heart catheterization data, which were collected at the first procedure after initiation. LVAD speed was recorded at time of right heart catheterization data. Right ventricular stroke work index (RVSWi) was calculated using 0.0136 × stroke volume index × (mean pulmonary artery pressure − mean right atrial pressure). Statistical analysis was performed utilizing a paired two-tailed *t*-test on Microsoft Excel (Microsoft®, Washington, USA).

Results

In total, eight patients were included with baseline demographics shown in *Table 1*. All patients had right ventricular failure refractory to medical therapy with diuretics and pump speed adjustments. The initial patients were trialled on oral milrinone at the end of life as a palliative intervention to facilitate discharge home or because of a lack of IV access. Subsequently, patients were started on milrinone to improve refractory symptoms while they awaited heart transplantation.

Oral milrinone was started a median of 1.5 [inter-quartile range (IQR) 1–2.3] years after LVAD implantation (*Table 2*). IV milrinone was established in three of the patients prior to oral milrinone initiation. The starting dose was a mean 6.4 ± 2.6 mg QDS and titrated up to 8.6 ± 4.7 mg QDS to achieve a mean milrinone level of 232.2 ± 153.4 ng/mL (tar-

Table 1 Patient demographics at time of LVAD implantation

Characteristic	*n* = 8
Female, no. (%)	1 (12.5)
Age at LVAD (mean years)	45.8 ± 12.8
Dilated cardiomyopathy, no. (%)	7 (87.5)
Ischaemic cardiomyopathy, no. (%)	1 (12.5)
Body mass index (mean kg/m^2)	24.9 ± 6.3
Serum eGFR (mean mL/min)	71.4 ± 30.5
Type 2 diabetes mellitus, no. (%)	2 (25)
NYHA (mean score)	3.3 ± 0.5
BNP (mean ng/L)	665.7 ± 451.5
TAPSE (mean cm)	12.8 ± 5.4
Cardiac index (mean L/min/m^2)	1.9 ± 0.4
PCWP (mean mmHg)	25.7 ± 13.9
PVR (mean Wood units)	4.1 ± 2.5

BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; LVAD, left ventricular assist device; NYHA, New York Heart Association functional classification; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; TAPSE, tricuspid annular plane systolic excursion.
Where appropriate, data are presented as ±standard deviation.

Table 2 Oral milrinone dosing, levels, time in therapeutic range, and duration of therapy

	n = 8
Duration after LVAD at time of oral milrinone initiation, median years (IQR)	1.5 (1–2.3)
IV milrinone prior to oral initiation, no. (%)	3 (37.5)
Initial milrinone dose (mean mg QDS)	6.4 ± 2.6
Final milrinone dose (mean mg QDS)	8.6 ± 4.7
Mean milrinone level (mean ng/mL)	232.2 ± 153.4
Time in therapeutic range, % (SD)	62.4 ± 18
Time below therapeutic range, % (SD)	15.4 ± 19.3
Time above therapeutic range, % (SD)	22.1 ± 13.4
Duration of oral milrinone therapy, median years (IQR)	1.2 (0.5–2.8)
Transplanted, no. (%)	2 (25)
Death, no. (%)	4 (50)
Continue with oral milrinone therapy, no. (%)	3 (37.5)

LVAD, left ventricular assist device; IQR, inter-quartile range; IV, intravenous; QDS, four times a day; SD, standard deviation.
Where appropriate, data are presented as ±SD.

get range 100–300 ng/mL). Median duration of oral milrinone therapy was 1.2 (IQR 0.5–2.8) years. TTR was 62.4 ± 18% with limitation of time above the therapeutic range to 22.1 ± 13.4%. Oral milrinone was only stopped because of transplantation (*n* = 2) or death (*n* = 3). One death occurred after transplantation, one death was secondary to LVAD infection, and the remaining two deaths were secondary to progressive right ventricular failure. Three patients continue oral milrinone therapy in the community.

In total, there were two adverse events detected. The first patient in the palliative cohort had several episodes of ventricular tachycardia detected by the implantable cardioverter defibrillator (ICD) that were not treated by the device. This occurred in the last few days of life when the patient was in multi-organ failure and the focus on palliative care. The second patient had an episode of ventricular fibrillation requiring ICD shock with successful cardioversion and no loss of consciousness. This patient also had a previous ICD shock 1 year prior to initiation of oral milrinone. In total, this was two adverse events over 14.25 years of treatment.

Table 3 Physiological effects of oral milrinone use

	Pre-oral milrinone		Post-oral milrinone		*P* value[a]
	Mean	SD	Mean	SD	
NYHA score	3.4	0.5	3.0	0.8	0.08
BNP (ng/L)	555	488.2	508.8	94.9	0.79
TAPSE (cm)	9.6	2.6	9.6	2.7	1.00
eGFR (mL/min)	53.9	27.8	50.8	31.8	0.55
CI (L/min/m^2)	1.9	0.3	2.2	0.5	0.34
PCWP (mmHg)	17.0	3.7	17.4	4.8	0.89
PVR (Wood units)	2.7	1.5	2.1	1.6	0.49
PASP (mmHg)	37.2	11.4	34.4	6.2	0.67
PADP (mmHg)	17.8	6.9	19.2	6.0	0.72
Mean PA (mmHg)	25.8	7.7	25.0	6.5	0.87
Wedge (mmHg)	17	3.7	17.8	5.1	0.80
Mean RAP (mmHg)	16.2	8.6	10.4	2.7	0.26
LVAD speed (r.p.m.)	2680.0	109.5	2740.0	230.2	0.53
SVi (mL/m^2)	28.3	5.7	29.3	4.7	0.78
RVSWi (g/m^2/beat)	3.8	2.0	5.8	2.7	0.16
PAPi (ratio)	1.4	0.8	1.5	0.3	0.79
RA/wedge	0.9	0.3	0.6	0.2	0.08

BNP, brain natriuretic peptide; CI, cardiac index; eGFR, estimated glomerular filtration rate; LVAD, left ventricular assist device; NYHA, New York Heart Association functional classification; PA, pulmonary artery; PADP, pulmonary artery diastolic pressure; PAPi, pulmonary artery pulsatility index; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PVR pulmonary vascular resistance; RA, right atrial; RAP, right atrial pressure; RVSWi, right ventricular stroke work index; SD, standard deviation; SVi, stroke volume index; TAPSE, tricuspid annular plane systolic excursion.
[a]Calculated using two-tailed paired *t*-test.

On the assessment of physiological changes, three palliative patients did not have post-initiation catheterization data, of which two also did not have brain natriuretic peptide measured and so were excluded from the analysis of these variables. There was no significant difference found after the initiation of oral milrinone on any of the physiological measures (*Table* 3); however, there were trends in reduction of New York Heart Association (NYHA) class from 3.4 ± 0.5 to 3.0 ± 0.8 (*P* = 0.08), reduction of right atrial/wedge pressure from 0.9 ± 0.3 to 0.5 ± 0.2 (*P* = 0.08), and improvement of RVSWi from 3.8 ± 2 to 5.8 ± 2.7 (*P* = 0.16). This trend to improved right ventricular functional parameters may have led to the trend in improvement of NYHA class functional status.

Conclusions

We report a small cohort of LVAD patients with right ventricular failure treated with oral milrinone. Firstly, our data show that oral milrinone can potentially be used safely in LVAD patients over a median duration of therapy of 1.2 (IQR 0.5–2.8) years. No patients discontinued therapy because of drug side

effects. We saw a small number of ventricular arrhythmia episodes (two events over 14.3 years of therapy). These patients are prone to arrhythmia for other reasons, and when they do occur, ventricular arrhythmias are generally well tolerated in the short term in LVAD patients.[10] Secondly, we did not see objective measures of physiological improvement but noted subjectively patients felt better judged by improvement in NYHA class. Finally, effective TDM allowed for 62% TTR and supported the safety profile.

We propose further randomized studies to establish the effect of oral milrinone on LVAD patient morbidity and mortality, including reducing heart failure hospitalization in refractory right ventricular failure.

Conflict of interest

None declared.

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