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Comparing the Effects of Milrinone and Olprinone in Patients with Congestive Heart Failure

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Abstract

Background: Phosphodiesterase-3 (PDE3) inhibitors are widely used among patients with congestive heart failure (CHF). However, no studies have compared the cardiovascular outcomes between different PDE3 inhibitors in CHF management. In this report, we retrospectively compared the clinical benefits of two PDE3 inhibitors, milrinone and olprinone, to determine which better controls the progression of CHF.

Methods: A total of 288 hospitalized patients who received PDE3 inhibitors [(milrinone; n = 77 and olprinone; n = 211, respectively)] for CHF were retrospectively enrolled. The primary endpoint was defined as having a major adverse cardiovascular and cerebrovascular event (MACCE) or cardiac death by day 60. Kaplan–Meier curves and multivariate Cox proportional models were used to compare the outcomes for patients treated with milrinone and olprinone.

Results: We found no significant differences in the baseline characteristics between the two groups. In patients treated with milrinone, a greater incidence of a MACCE or cardiac death was observed (log rank; P = 0.005 and P = 0.01, respectively). Milrinone-treated patients with ischemic heart disease and chronic

kidney disease (CKD) at stage ≥4 presented with greater incidence of MACCE (log rank; P < 0.001 and P = 0.006, respectively). Similarly, these patients were significantly more likely to succumb to cardiac death (log rank; P < 0.001 and P = 0.02). Multivariate Cox proportional hazard models demonstrated that milrinone treatment was an independent predictor of MACCE [hazard ratio (HR) 3.17; 95%CI, 1.64–6.10] and cardiac death (HR 2.64; 95%CI, 1.42–4.91). Oral administration of a β-blocker at discharge occurred more often in the olprinone-treated patients than in the milrinone-treated patients (63% vs. 29%, P = 0.004).

Conclusions: We compared the outcomes of milrinone and olprinone treatment in patients with CHF. Those treated with milrinone were more likely to succumb to a MACCE or cardiac death within 60 days of treatment, which was especially true for patients with ischemic heart disease or CKD.

Key words; Phosphodiesterase-3 inhibitor, Heart failure, Ischemic heart disease, Chronic kidney disease

Introduction

Positive inotropes such as dobutamine and phosphodiesterase-3 (PDE3) inhibitors are a common part of the management protocol for patients experiencing an episode of acute congestive heart failure (CHF) as these drugs help maintain blood pressure and cardiac output during unstable hemodynamics.[1] Therefore, such drugs should be considered for patients with severe hemodynamic compromise and low cardiac output.[2] PDE3 inhibitors prevent the degradation of cyclic adenosine monophosphate, thereby increasing its cellular concentration. PED3 inhibitors enhance myocardial contractility and dilate vascular smooth muscle by increasing cAMP levels, resulting in increased cardiac output and reduced mean pulmonary artery and pulmonary capillary wedge pressures relative to an increase in heart rate.[3, 4] The positive inotropic action of PDE3 inhibitors is not a result of direct beta adrenergic receptor stimulation in myocardial cells. This allows the prescription of β-blockers for heart failure (HF). The unique mechanism underlying PDE3 inhibitors makes them the preferred inotrope for patients with advanced HF who are also prescribed β-blockers. In Japan, the PDE3 inhibitors milrinone and olprinone are typically used

clinically to treat patients with CHF. Olprinone was developed in Japan (Eisai, Tokyo, Japan) for the clinical management of patients with CHF. As compared to milrinone, it uniquely exhibits direct vasodilatory actions of small arteries in the peripheral organs.[5-7] In particular, olprinone is reported to directly increase renal blood flow. However, the action of milrinone on renal blood flow is mostly affected by cardiac output.[8, 9] Therefore, olprinone may be more beneficial than milrinone for treating HF in patients with CKD. Moreover, the difference in the half-life period between these two drugs may influence their clinical outcomes. Adverse effects such as hypotension, atrial fibrillation, and arrhythmia commonly occur after the use of PDE3 inhibitors. Considering the difference in pharmacokinetics and hemodynamic effects, particularly in the peripheral organs, olprinone may be more beneficial than milrinone in patients with HF. However, no study has compared the management outcomes of these two drugs in patients with CHF.

Therefore, we compared the clinical benefits of milrinone and olprinone to determine which of these two PDE3 inhibitors more effectively controls the symptoms of CHF.

Materials and Methods

Study population

Initially, we retrospectively assessed the clinical data obtained between January 2007 and January 2017 for 2608 patients who were hospitalized with CHF. Of these, 288 patients who were intravenously administered olprinone (n = 211) or milrinone (n = 77) as a part of their initial treatment were included in the final study cohort. The exclusion criteria were cardiac arrest on admission, introduction of percutaneous cardiopulmonary support, and kidney failure treated with dialysis. The initial intravenous infusion dose was 0.125–0.75 μg/kg/min for milrinone and 0.05–0.4 μg/kg/min for olprinone. No loading infusion was given. The administration of PDE3 inhibitors was terminated at improved pulmonary congestion confirmed by physical assessment and X-ray imaging. Dosage adjustment and discontinuation of the PDE3 inhibitor due to an adverse effect, including hypotension, lethal arrhythmia, and worsening of renal failure were at the discretion of the attending physicians. The clinical characteristics and outcomes of the patients who received olprinone and those who received milrinone were compared. We conducted the study according to the guidelines of

the Declaration of Helsinki, and it was approved by the Ethics Committee of the Toho University School of Medicine, Tokyo, Japan.

Clinical characteristics

Demographic and clinical data of the patients that were collated at hospitalization were obtained from the medical records. The baseline data included age, sex, New York Heart Association Class III or IV status, and the statuses of hypertension, diabetes mellitus (DM), dyslipidemia, atrial fibrillation, and ischemic heart disease (IHD). The latter was defined as a previous percutaneous coronary intervention, acute myocardial infarction, previous coronary artery bypass graft, and peripheral artery disease. Laboratory data obtained upon admission were as follows: hemoglobin, serum sodium and potassium, blood urea nitrogen, creatinine, estimated glomerular filtration rate and B-type natriuretic peptide (BNP), blood pressure (BP), ejection fraction, and medications such as diuretics, angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), β-blockers, aldosterone receptor antagonists (ARA), and calcium channel blockers (CCB).

Optimal medical therapy for CHF, including administration of diuretics, ACE-I, ARB, β-blockers, ARA, and CCB, was suggested as an additional treatment after admission. The follow-up procedures that occurred after the administration of a PDE3 inhibitor included monitoring of the BP, possible atrial fibrillation of each patient, and noting the occurrence of lethal arrhythmia.

The primary endpoint for the patients was taken as a major, adverse cardiovascular and cerebrovascular event (MACCE), defined as cardiac death, acute coronary syndrome, lethal arrhythmia including sustained ventricular tachycardia and ventricular fibrillation, HF requiring re-hospitalization, and stroke, or cardiac death within 60 days of the initial injection of the PDE3 inhibitor. Secondary endpoints included hypotension, lethal arrhythmia or atrial fibrillation while using PDE3 inhibitors.

Statistical analysis

The data were analyzed using a statistical package for R (R Development Core Team, Vienna, Austria). Continuous variables were expressed as mean ± standard deviation or median and interquartile range. Categorical variables were presented as absolute values or percentages and were compared using Fisher's exact or chi-square tests as appropriate. The event rates for MACCE, cardiac death, and MACCE and cardiac death for patients with or without IHD were determined using Kaplan–Meier estimates. Finally, the rates between groups were compared using log-rank tests. The multivariate Cox proportional hazards models were used to evaluate the independent predictor of MACCE after adjusting for the variables with P-values of <0.10 obtained by univariate analysis and clinically important patient characteristics. The results were expressed as the hazard ratio (HR) and its 95% confidence interval (CI). Differences were considered significant at $P < 0.05$.

Result

Our retrospective study enrolled 288 patients with CHF (165 males, mean age 70.2 ± 15.4 years) who were hospitalized and subsequently treated with olprinone (211 patients, 117 males, 70.5 ± 15.0 years) or milrinone (77 patients, 48 males, 69.5 ± 16.5 years). The baseline characteristics of the patients are presented in Table 1. The clinical demographics, including age, sex, New York Heart Association classification, BP values, medical history, and laboratory data, were similar between the two treatment groups. Although the BNP values were greater for the milrinone group, they were not significantly different (P = 0.06). Regarding cardiac medications, administration of diuretics (ACE-I, ARB, ARA, ß-blockers, and CCB) was similar in both groups. The transthoracic echocardiography of the patients showed a similar range of left ventricular ejection fractions. Despite the administration of a PDE3 inhibitor, a MACCE (n= 100), cardiac death (n=57), HF requiring re-hospitalization (n=31), lethal arrhythmia (n=7), stroke (n=3) or acute coronary syndrome (n=2), was occurred within 60 days, respectively. The incidence of MACCE (48.1% vs. 29.9%, P < 0.01) and cardiac death (28.5% vs. 12.6%, P = 0.02) were significantly more common among patients treated with

milrinone than in those treated with olprinone. The Kaplan–Meier plots demonstrated an increased number of MACCE (P = 0.005) and cardiac deaths (P = 0.01) occurred in patients treated with milrinone than in those treated with olprinone (Figs. 2A, B). In patients with and without IHD, the event-free rates of MACCE and cardiac deaths were significantly lower for the milrinone subgroup with IHD (Figs. 3A, B) than the other subgroups. In patients with and without CKD stage ≥4, event-free rates of MACCE and cardiac deaths were significantly lower for patients treated with milrinone and at CKD stage ≥4 (Figs. 4A, B) than the other subgroups. The multivariate Cox proportional hazard models showed that age, positive IHD status, renal dysfunction, BNP, and milrinone treatment were independent predictors of MACCE (Table 2). The forest plots of clinical outcomes for MACCE and cardiac deaths according to patient risk profiles for the two treatment groups are shown in Figure 5. Among patients with a greater than average risk profile (aged ≥75 years and positive for hypertension, diabetes, dyslipidemia, IHD, BNP, and progressive CKD) an increased incidence of MACCE was significantly greater for patients treated with milrinone than with olprinone (Fig. 5A). Similar findings were observed for both groups regarding cardiac death. Among patients who were ≥75 years of age or with diabetes, IHD,

a larger BNP value, or progressive CKD, cardiac death was more common for those in the milrinone group (Fig. 5B). Regarding secondary endpoints, significant differences between two groups were not found for the lethal arrhythmia (1.4% vs. 2.5%, olprinone vs. milrinone treatment; P = 0.61) and atrial fibrillation (4.2% vs. 3.8%, P = 0.91). Hypotension that required intervention was significantly more common for the milrinone-treated patients (1.4% vs. 9.0%, P = 0.004).

Discussion

To our knowledge, this is the first study comparing the clinical impact of milrinone and olprinone treatments on patients with CHF. Our data demonstrates that patients treated with milrinone had higher incidences of MACCE than those treated with olprinone. Moreover, the trends of increased MACCE risk and cardiac death were observed for milrinone-treated patients with IHD and CKD. In comparison with olprinone-treated patients, fewer milrinone-treated patients were treated with a β-blocker at discharge.

Various benefical effects induced by positive PDE3 inhibitors, including anti-inflammatory effects, decreased myocardial infarct size, increased renal blood flow, and vasodilation of small arteries have been reported.[6-12] However, recent guidelines have defined PDE3 as a class IIb indication for patients with IHD.[13, 14] The OPTIME-CHF (The Outcomes of Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure) trials showed that the routine use of intravenous milrinone was not recommended.[13] In particular, intravenously administered milrinone was associated with higher re-hospitalization rates and mortality among patients with IHD than those without IHD.[14] A total of 35% of the patients in our study had IHD and we observed that milrinone-treated patients with greater risk profiles (i.e., elderly patients or patients positive for dyslipidemia, DM, IHD, or CKD) were more likely to experience MACCE and cardiac death. Patients with IHD may have chronic ischemic hibernating myocardium that is associated with increased heart cell apoptosis, which may progress to HF when treated with milrinone.[14-17] Another reason for a greater susceptibility of patients with IHD to lethal arrhythmia is the potential for re-entry around areas of myocardial scars when treated with milrinone.[18] In accordance with this, our study revealed that the incidence of lethal arrhythmia was significantly greater in

patients with IHD treated with milrinone than those treated with olprinone (3.2% vs. 1.3%, P = 0.049). As milrinone has a longer half-life and olprinone has a greater impact on increasing renal blood flow, the use of olprinone may be safer than milrinone among patients with HF who have CKD complications. Accordingly, comorbid CKD increases with the progression of HF.[19, 20] Therefore, we intend to target more complex and exacerbated cases of patients with HF who require inotropy and vasodilation by olprinone in a future study.

We importantly found that milrinone-treated patients were significantly less likely to be prescribed a β-blocker at discharge, which is a conventional treatment for chronic HF, than olprinone-treated patients. β-blocker treatment has a significant positive impact on the survival of patients with chronic HF, as proven in large-scale clinical trials.[21-24] Metra and colleagues proposed that PDE3 inhibitor treatment may allow the successful initiation and upward titration of a β-blocker.[25] However, combining dobutamine and a β-blocker, such as carvedilol, is thought to exacerbate poor hemodynamics of patients with HF. A number of studies report that concurrent β-blocker and PDE3 inhibitor treatments for patients with chronic HF are effective[26-29] because the hemodynamic response

to the PDE3 inhibitor was maintained or enhanced by the administered β-blocker (metoprolol or carvedilol).[25] Interestingly, we found that the oral administration of a β-blocker at discharge significantly occurred more frequently for olprinone-treated patients than milrinone-treated patients (63% vs. 29%, P = 0.004). This suggests that milrinone treatment may negatively affect BP in patients with HF than olprinone treatment. Clinically, the coadministration of a β−-blocker with milrinone in patients with HF should be limited due to the effect of the latter on low BP. We found that more olprinone-treated patients received β-blocker initiation or addition during and after the PDE3 inhibitor administration(18.4% vs. 3.8%, P = 0.0015). Furthermore, olprinone is reported to have more potent vasodilatory effects with greater inducible cardiac output than milrinone.[30, 31] In contrast to the difference in β-blocker dose, the BP at discharge was similar between the groups (Olprinone: sBP 105 ± 19.7 mmHg, dBP 58.4 ± 10.6 mmHg vs. Milrinone: sBP 104.1 ± 19.4 mmHg, dBP 59.1 ± 19.4 mmHg). We observed that hypotension requiring intervention was more common among the milrinone-treated patients than those treated witholprinone. Based on our 60-day observation period, the olprinone-treated patients could benefit from treatment with a β-blocker, with a reduction in the risk of MACCE, compared with the

milrinone-treated patients. Although the safety and effectiveness of the routine use of a PDE3 inhibitor along with a β-blocker has not been proven, it may be essential for preventing future cardiovascular events in certain patients with chronic HF.

Study limitations

Limitations of this study include its retrospective nature, the dependence of treatments of HF among patients on the judgment of the attending doctor, and the non-quantitative nature of the effect of administered PDE3 inhibitors. Olprinone treatment has not been studied in a large-scale clinical trial, whereas milrinone has been studied. Therefore, the short- and long-term clinical effects of olprinone treatment are not known. Although, the effectiveness of short-term concurrent therapies with a ß-blocker and a PDE3 inhibitor has been examined, we did not provide detailed information including the types and dosages of the prescribed ß-blocker. Hence, a long-term clinical evaluation of the concurrent use of a ß-blocker and a PDE3 inhibitor is needed. A critical limitation of our study is that we did not compare patients with HF treated with or without a PDE3 inhibitor.

The OPTIME-CHF study has previously demonstrated that milrinone did not improve the death and hospitalization rates compared to a placebo.[13] While we did not directly compare milrinone and olprinone, our data suggests that olprinone may reduce the incidence of MACCE and cardiac deaths due to an increased use of β-blockers. Finally, because of a limited number of MACCE events, sub-analyses of the association between PDE3 inhibitor and MACCE e.g HF requiring re-hospitalization, were not assessed.

Conclusion

In this study, administration of milrinone was associated with a greater incidence of MACCE and cardiac deaths than olprinone treatment. Furthermore, negative events were greater with CKD as it progressed in the milrinone-treated patients. Our data may contribute to future guidelines that suggest the optimal choice of a PDE3 inhibitor in HF management. We found that milrinone-treated patients experienced an increased incidence of MACCE than olprinone-treated patients. This was more evident in milrinone-treated patients with IHD or CKD.

Conflicts of interest

T.I. received grant support from Bristol-Myers Squibb Bayer Healthcare, Medtronic Japan, Japan Lifeline and Daiichi Sankyo and lecture fees from Bayer Healthcare, Bristol-Myers Squibb, Pfizer, Daiichi Sankyo and Ono Pharmaceutical. The other authors report no conflicts of interest.

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Figure legends

Figure 1. Study flow chart. HF; heart failure, PDE; phosphodiesterase, MACCE; all cause of death, cardiac death, lethal arrhythmia, re-hospitalization

Figure 2. Kaplan-Meire curves of cumulative event rates.
Kaplan-Meire curves shows MACCE and cardiac death of milronone and olprinone after 60 days. A) MACCE, B) cardiac death,
MACCE; all cause of death, cardiac death, lethal arrhythmia, re-hospitalization

Figure 3. Kaplan-Meire curves of cumulative event rates.
Kaplan-Meire curves shows MACCE and cardiac death of milronone and olprinone with or without IHD after 60 days. A) MACCE, B) cardiac death
MACCE; all cause of death, cardiac death, lethal arrhythmia, re-hospitalization
IHD; ischemic heart disease

Figure 4. Kaplan-Meire curves of cumulative event rates.
Kaplan-Meire curves shows MACCE and cardiac death of milronone and olprinone with CKD stage <4 or with CKD stage ≥4 after 60 days. A) MACCE, B) cardiac death
MACCE; all cause of death, cardiac death, lethal arrhythmia, re-hospitalization
CKD; chronic kidney disease

Figure 5. Forest plot of clinical outcomes for (A) MACCE and (B) cardiac death: olprinone vs milrinone group.
CAD, coronary artery disease; BNP, Brain natriuretic peptide; CKD, chronic kidney disease.

Table 1. Baseline Patients Characteristics

Variables	*Olprinone*	*Milrinone*	*p value*
n	211	77	
Age (yrs)	70.5 ± 15.0	69.5 ± 16.5	0.63
Men (%)	117 (55.4)	48 (62.3)	0.34
NYHA classification (%)	Ⅲ:52.1 Ⅳ:23.3	Ⅲ:54.5 Ⅳ:22.1	0.78
Blood pressure at hospitalization			
Systolic, mmHg	111.9 ± 18.3	109.1 ± 19.1	0.26
Diastolic, mmHg	63.2 ± 13.4	62.7 ± 13.3	0.57
mean, mmHg	72.1 ± 8.2	71.1 ± 7.8	0.31
Blood pressure at discharge			
Systolic, mmHg	105.1± 19.7	102.1 ± 19.4	0.29
Diastolic, mmHg	58.4 ± 10.6	59.1 ± 19.4	0.53
mean, mmHg	69.1 ± 6.9	68.2 ± 6.5	0.46
Medical history, n (%)			
Hypertension	144 (68.2)	53 (68.8)	0.91
Diabetes mellitus	82 (38.8)	29 (37.6)	0.89
Dyslipidemia	43 (20.3)	14 (18.1)	0.74
Atrial fibrillation	59 (27.9)	16 (20.7)	0.28
Ischemic heart disease	70 (33.1)	31 (40.2)	0.68
Myocardial infarction	33 (15.6)	7 (9.0)	0.18
Previous CABG	6 (2.8)	3 (3.8)	0.70
Peripheral arterial disease	23 (10.9)	11 (14.2)	0.41

Dilated cardiomyophathy	13 (6.1)	8 (10.0)	0.31
Previous valve replacement	7 (3.3)	4 (5.1)	0.67
Laboratory data			
Hemoglobin, g/dL	12.0 ± 2.1	11.8 ± 2.15	0.55
Sodium,mg/dL	137.8 ± 5.0	137.1 ± 5.4	0.83
Potassium, mg/dL	3.95 ± 0.49	4.06 ± 0.52	0.25
Urea nitrogen, mg/dL	24.7 ± 13.7	25.4 ± 14.6	0.75
Creatinine, mg/dL	1.10 ± 0.52	1.17 ± 0.66	0.37
eGFR, ml/min./1.73m^2	54.8 ± 24.0	54.1 ± 24.5	0.82
Brain natriuretic peptide, pg/dL	1062.3 ± 961.2	1049.7 ± 959.1	0.06
Ejection Fraction. %	44.2 ± 18.8	41.7 ± 19.1	0.31
Medications, n (%)			
Diuretics	92 (43.6)	40 (51.9)	0.23
ACE inhibitors/ARBs	87 (41.2)	34 (44.1)	0.28
β-Blockers	60 (28.4)	24 (31.1)	0.66
Aldsterone antagonists	21 (9.9)	9 (11.6)	0.65
Calcium channel blockers	38 (18.0)	10 (12.9)	0.37
Duration of hospitalization	17.8±11.8	19.9±15.7	0.21
Duration of PDE inhibitor treatment	6.6±1.79	6.77±2.01	0.48

Abbreviations: CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; ACE, angiotensin-converting enzyme inhibitors; ARB,angiotensin-receptor blockers

Table2. Multivariate predictors of (A) MACCE and (B) cardiac death

(A)

Multivariate analysis	*HR*	*95% CI*	*p value*
Age	2.4	1.25-4.63	0.008
Hypertension	0.38	0.18-0.77	0.07
Diabetes mellitus	1.35	0.68-2.64	0.38
Dyslipidemia	0.44	0.19-1.03	0.06
Atrial fibrillation	1.3	0.65-2.58	0.45
Ischemic heart disease	4.23	2.02-8.82	<0.001
Brain natriuretic peptide	3.9	1.68-9.08	0.001
Ejection fraction	0.78	0.35-1.72	0.53
Renal dysfunction	4.06	1.79-9.20	<0.001
Milrinone	3.17	1.64-6.10	<0.001

(B)

Multivariate analysis	*HR*	*95% CI*	*p value*
Age	1.46	0.58-3.59	0.41
Hypertension	0.41	0.21-0.83	0.01
Diabetes mellitus	1.33	0.71-2.47	0.37
Dyslipidemia	0.42	0.19-0.94	0.03
Atrial fibrillation	1.23	0.64-2.34	0.52
Ischemic heart disease	3.36	1.75-6.43	<0.001
Brain natriuretic peptide	2.92	1.39-6.11	0.004

Ejection fraction	0.8	0.39-1.61	0.53
Renal dysfunction	5.61	1.09-28.9	0.03
Milrinone	2.64	1.42-4.91	0.002

Abbreviations: MACCE, Major adverse cardiac and cerebrovascular event