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CASE REPORT

The Use of Midodrine in Patients With Advanced Heart Failure

In many patients, the treatment of heart failure (HF) cannot be optimized because of pre-existing or treatment-induced hypotension. Midodrine, a peripheral α1-adrenergic agonist may allow for up-titration of neurohormonal antagonist therapy leading to improved outcomes. Ten consecutive patients with HF due to systolic dysfunction and symptomatic hypotension interfering with optimal medical therapy were started on midodrine. After a 6-month follow-up, a higher percentage of patients were on optimal HF therapy (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker mg % of optimal dose 20% vs 57.5%; P<.001) (β-blockers mg % optimal dose 37.5% vs 75%; P<.001) (spironolactone/eplerenone mg % 43.7% vs 95%; P<.001). This led to an improvement in left ventricular ejection fraction (baseline 24±9.4 vs 32.2±9.9; P<.001) and clinical outcomes, with a significant reduction in total hospital admissions (32 vs 12; P=.02) and total hospital days (150 vs 58; P=.02). Congest Heart Fail. *2009;15:1–4.*

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There are approximately 5 million Americans living with heart failure (HF) and 550,000 new cases are diagnosed annually.[1] In addition, these patients account for nearly 7 million hospital days each year and nearly 300,000 deaths annually.[2] The treatment of HF has greatly evolved over the past few decades with the use of neurohormonal-blocking agents such as angiotensin-converting enzyme (ACE) inhibitors,[3–5] certain β-blockers (metoprolol succinate, carvedilol, and bisoprolol),[6–8] angiotensin receptor blockers (ARBs),[9,10] and aldosterone antagonists that reduce mortality. The use of ACE inhibitors is associated with a 17% to 25% reduction in mortality,[2–5,11] while β-blockers reduce mortality by 34% to 65%.[2,6–8] Despite the wealth of scientific evidence supporting the use of neurohormonal blockade, they remain underused.

National data on outpatient use of ACE inhibitors have shown an improvement of its use from 24% to only 38% from 1990 to 2002. [12] The Acute Decompensated Heart Failure Registry (ADHERE)[13] showed that the use of β-blockers was only 47% in patients admitted to the hospital with a previous diagnosis of HF due to systolic dysfunction. More recent data from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) registry[14] including nearly 50,000 patients hospitalized with HF demonstrated that the use of ACE inhibitors and β-blockers were both 83%.

Although the use of ACE inhibitors and β-blockers has improved dramatically, there are still a significant number of patients who are not being treated largely due to low blood pressure. An increase in blood pressure may allow tolerance of neurohormonal-blocking agents and improved outcomes in such patients. Midodrine is a peripheral α_1-adrenergic agonist that is approved by the US Food and Drug Administration for the treatment of orthostatic hypotension. It has been safely and successfully used in patients with end-stage kidney disease whose hypotension would otherwise have compromised chronic dialysis.[15] Furthermore, it was successfully used to treat hypotension secondary to stunned myocardium post-infarction.[16] Its use in patients with HF is not known. We conducted a study to determine whether the use of midodrine is safe in HF patients and would allow optimization of medical therapy and thus improved outcomes in patients in whom therapy is limited due to symptomatic hypotension.

Methods

Study Population. This study prospectively studied 10 consecutive patients with HF due to systolic dysfunction (left ventricular ejection fraction [LVEF] ≤35%) and symptomatic hypotension (systolic blood pressure <85 mm Hg with either dizziness or lightheadedness) interfering with optimal medical therapy. Patients were excluded if they had severe valvular dysfunction, heart rate <40 beats per minute, or liver failure or were undergoing hemodialysis.

Study Protocol. Therapy with midodrine was initiated at a dose of 5 mg orally every 6 hours and increased to a maximum of 10 mg every 6 hours.

Table I. Patient Characteristics

Characteristics	(N=10)
Sex	
Male	8 (80%)
Female	2 (20%)
Age, y	63.3±18
Weight, lb	179±56
Coronary artery disease	5 (50%)
CKD (GFR <60 mL/min/1.73 m^2)	9 (90%)
Diabetes mellitus	3 (30%)
Previous HTN	3 (30%)
COPD	1 (10%)
Systolic dysfunction (LVEF <40%)	10 (100%)
RV failure (Bi-V failure)	5 (50%)

Abbreviations: Bi-V, bi-ventricular; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; GFR, glomerular filtration rate; HTN, hypertension; LVEF, left ventricular ejection fraction; RV, right ventricular.

Blood pressure, B-type natriuretic peptide (BNP) levels, and medical therapy were recorded at inclusion and at 6 months. Transthoracic echocardiography was performed within 6 months prior to study enrollment and 6 months afterwards. The number of hospital admissions and hospital days were recorded before and during treatment. Background diuretic therapy was adjusted according to volume status. The Modification in Diet in Renal Disease (MDRD) formula was used to estimate glomerular filtration rate at baseline and after 6 months of therapy.

Statistical Analysis. A P value $<.05$ was considered statistically significant. Comparisons were made using Student t test.

Results

Patient's baseline characteristics are shown in Table I. Of the 10 patients, 50% had ischemic cardiomyopathy and 50% had concomitant right ventricular failure. Measured outcomes at baseline and at 6-month follow-up are listed in Table II and shown in Figure 1. At 6 months, patients had a significant increase in blood pressure and improvement in functional class, and a higher percentage of patients were on optimal HF therapy. Also, significant reductions in BNP and left ventricular end-diastolic diameter (LVEDD) with a significant increase in LVEF were noted (Figure 2). Clinical outcomes were improved as well, with a statistically significant reduction in total hospital days and hospital admissions.

Adverse Effects. Midodrine was well tolerated with no reported side effects in these 10 patients. However, other non-study patients who we have treated with coexisting benign prostatic hypertrophy have developed prostatism on rare occasions, which was mitigated with dose reduction.

Discussion

This study demonstrated that the addition of midodrine in HF patients with symptomatic hypotension allowed optimization of medical therapy with neurohormonal agents, leading to reverse remodeling and improved outcomes. The benefits of optimal HF therapy in such patients appear to offset any potential adverse effects due to the vasoconstrictive effects of midodrine. The patient population included in this study had advanced HF (90% New York Heart Association [NYHA] class III or IV). These patients have a high mortality and would receive the most benefit from neurohormonal-blocking agents. However, the mean blood pressure in this group was 79.2±4.6 mm Hg, making it difficult to achieve the desired dose of ACE inhibition and β-blockade due to symptomatic hypotension used in clinical trials to reduce mortality. Symptomatic hypotension is a common occurrence in patients with advanced HF.

Table II. Measured Outcomes

	Baseline	6 Months	P Value
Midodrine	100%	90%	
SBP, mm Hg	79.2±4.6	99±11	<.0004
DBP, mm Hg	49.1±4.2	58.8±4.9	<.0002
NYHA class	3.4 (class IV, 5; class III, 4; class II, 1; class I, 0)	2.4 (class IV, 1; class III, 4, class II, 3; class I, 2)	<.001
BNP, pg/mL	1402±1559	706±592	<.0001
GFR, mL/min/1.73 m^2	47.1±8.4	42.8±7.2	NS
ACE/ARB use	50%	90%	<.001
ACE/ARB mg % of optimal dose[a]	20%	57.5%	<.001
β-Blockers use	80%	100%	<.01
β-Blocker mg % of optimal dose[b]	37.5%	75%	<.001
Aldactone/eplerenone use	70%	90%	<.001
Aldactone/eplerenone mg % of optimal dose[c]	43.7%	95%	<.001
LVEDD, cm	6.22±0.75	5.9±0.87	<.04
LVEF, %	24±9.4	32.2±9.9	<.001
Total hospital admissions	32 (6 mo prior to enrollment)	12 (within the 6 mo of the study period)	.02
Total hospital days	150	58	.02

Abbreviations: BNP, B-type natriuretic peptide; DBP, diastolic blood pressure; GFR, glomerular filtration rate; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure. [a]Optimal dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) was considered equivalent to 20 mg of lisinopril daily or 100 mg of losartan. [b]Optimal dose of β-blocker was considered equivalent to carvedilol 25 mg twice daily. [c]Optimal dose of spironolactone was 25 mg daily, and eplerenone was 50 mg daily.

In the Assessment of Treatment With Lisinopril and Survival (ATLAS) trial,[17] which looked at the tolerability of high-dose ACE inhibitors in patients with chronic HF, hypotension/dizziness occurred in 12.8% in the high-dose group (32.5 or 35.0 mg of lisinopril) and 9% in the low-dose group (2.5 or 5.0 mg). Furthermore, in patients considered to be at high risk for adverse effects (systolic blood pressure <120 mm Hg, serum creatinine ≥1.5 mg/dL, age ≥70 years, and patients with diabetes requiring hypoglycemic therapy), the incidence of hypotension/dizziness occurred in approximately 35% of patients in the high-dose group and 23% in the low-dose group. Although the incidence of hypotension/dizziness was common, it led to drug withdrawal in approximately 2% of the patients in the study. It should be noted, however, that these patients were followed frequently due to study protocol and may differ from clinical practice. The incidence of hypotension and dizziness may be higher with β-blockers. Butler and colleaguges[18] studied 206 patients with systolic HF in clinical practice and found that dizziness occurred in 41% of patients and hypotension in 28% of patients. Hypotension was the reason for discontinuation of therapy in 28% of the 51 (19%) patients with treatment failures. Twenty-two (55%) of these treatment failures were overcome by switching to a different β-blocker.

In an attempt to overcome difficulties in up-titration of neurohormonal-blocking agents due to symptomatic hypotension, we started this cohort on midodrine at a dose of 5 mg every 6 hours with an increase to 10 mg every 6 hours. The dose was well tolerated, with no reported adverse effects. At the end of 6 months, the significant increase in neurohormonal blockade, ie improvement in HF therapy, translated into significant improvement in reverse remodeling manifested by a reduction in LVEDD and an increase in LVEF. This was associated with improvement in clinical outcomes, including number of hospitalizations and length of stay, which have been independently associated with early re-admissions for HF and increased 30-day and 1-year mortality.[19] A low systolic blood pressure often exacerbates pre-existing renal insufficiency in patients with HF. In our cohort of patients, the use of midodrine was associated with preservation of kidney function (no significant change in glomerular filtration rate using the MDRD formula).

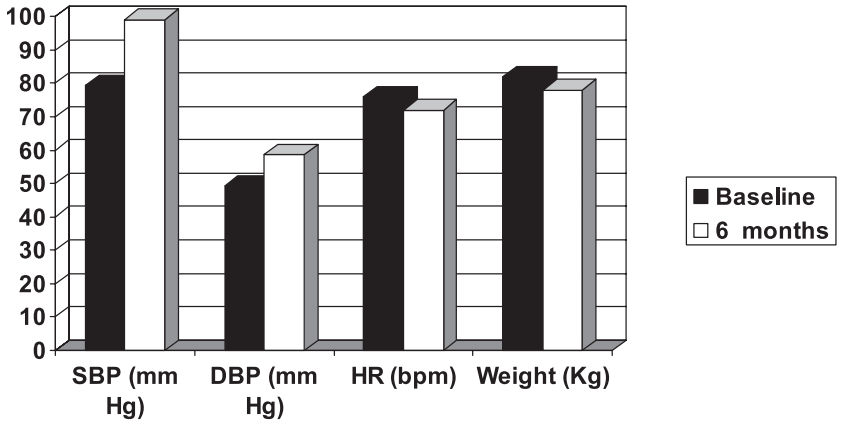

Figure 1. Clinical data pre-midodrine and post-midodrine treatment. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; bpm, beats per minute.

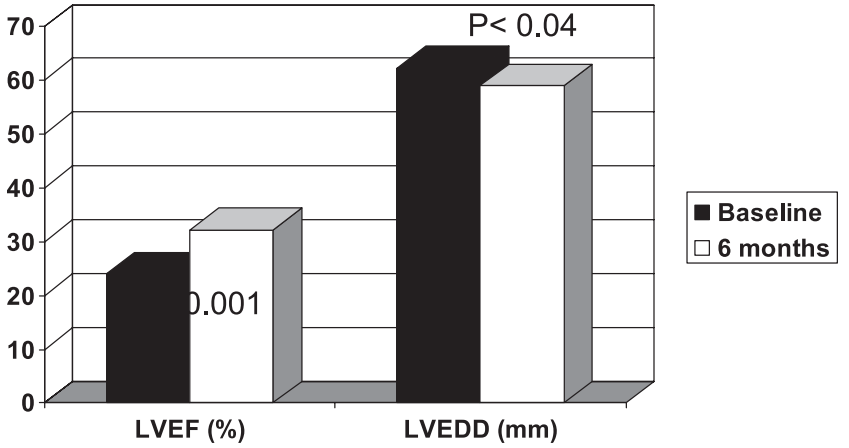

Figure 2. Left ventricular ejection fraction (LVEF) and left-ventricular end-diastolic diameter (LVEDD) pre-midodrine and post-midodrine treatment shows evidence of reverse remodeling.

Conclusions

The use of midodrine was well tolerated in our small cohort of patients with advanced HF and allowed for up-titration of neurohormonal-blocking agents in patients with symptomatic hypotension, leading to reverse remodeling and improved clinical outcomes. Further large-scale studies are warranted to determine whether a benefit will be seen in a similar patient population.

Disclosures: Dr Berkowitz is an investigator and speaker for Scios, Inc and Biosite, Inc.

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