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Midodrine to optimize heart failure therapy in patients with concurrent hypotension

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Abstract

According to the Centers for Disease Control and Prevention statistics, about 6.2 million adults in the United States have heart failure. Guideline-Directed Medical Therapy (GDMT) involving the use of renin-angiotensin-aldosterone system inhibitors with or without a neprilysin inhibitor, β-blockers, mineralocorticoid-receptor-antagonists, and sodium-glucose cotransporter-2 inhibitors serve as the backbone for heart failure with reduced ejection fraction (HFrEF) therapy. However, in patients with refractory hypotension, the initiation of GDMT may not be possible. We present four cases where the use of midodrine, an alpha adrenergic agonist, serves as bridge therapy for the initiation or continuation of GDMT with marked clinical improvement. These cases illustrate how exacerbations of HFrEF may be ameliorated with outpatient midodrine titration among patients with baseline, persistent hypotension such that GDMT may be better tolerated.

Keywords

Midodrine, heart failure, guide directed medical therapy, dose titration

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Introduction

According to the Centers for Disease Control and Prevention statistics, about 6.2 million adults in the United States have heart failure. Guideline-Directed Medical Therapy (GDMT) involving the use of renin-angiotensin-aldosterone system inhibitors with or without a neprilysin inhibitor, β-blockers, mineralocorticoid-receptor-antagonists, and sodium-glucose cotransporter-2 inhibitors serve as the backbone for heart failure with reduced ejection fraction (HFrEF) therapy.[1] Treating and optimizing care of select populations with persistent hypotension such as those with chronic heart failure can be challenging as many of the aforementioned classes of medications reduce blood pressure.[2–4] Midodrine, an alpha adrenergic agonist approved nearly 20 years ago, through its action as a peripheral vasoconstrictor, has seen use in the treatment of orthostatic hypotension (OH) as well as the reduction of intravenous vasopressor requirement in the intensive care unit (ICU).[5–7] Recent meta-analysis and retrospective observational studies, however, have revealed only a limited role of midodrine in the treatment of OH and paltry evidence to reduce intravenous vasopressor requirements.[8–10] These studies collectively therefore highlight a constrained role of midodrine as a direct pharmacological bolster for cardiogenic hypotension at least within the confines of fixed-dose regimens on which most of these conclusions are based. Nonetheless, there is widespread use and thus the potential for applications in difficult situations such as the HFrEF cases described in this series. In addition, new research has proposed promising mechanisms through which midodrine may act in the context of cardiac remodeling, which may indirectly improve cardiac contractility through agonism of alpha 1 A subtype adrenergic receptor.[11] Of course, an increase in afterload is one theoretical concern among those with cardiac insufficiency especially with the use of nonselective alpha 1 agonism. Montgomery et al.[12] have revealed, however, selective low dose alpha 1 A subtype agonism preserved and improved cardiac function among doxorubicin-induced cardiomyopathy models. Indeed, more recent studies have seen promising results of alpha 1 agonist therapy such as A61603 and dabuzalgron to restore left and right ventricular failure in rodent models.[13]

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Table 1. Treatment Regimens, Duration, and Final LVEF.

Patient	Age	Gender	Pre-treatment LVEF (%)	Dose of midodrine	Dosing approach	Duration of midodrine from pre-treatment through post-treatment	Post-treatment LVEF (%)
1	56	Male	35	2.5 mg BID to 10 mg TID	2.5 mg BID incremental increase up to 10 mg TID with decrease down to 5 TID, proceeding to BID to once daily dosing until discontinuation	24 months	52
2	58	Female	18	2.5 mg BID to 5 mg TID	2.5 mg incremental increase with complete and immediate discontinuation	2 months	53
3	61	Female	30	2.5 mg BID to 5 mg TID	2.5 mg BID to TID then increase to 5 mg TID with immediate complete discontinuation	1 month	40
4	57	Female	31	5 mg BID to TID then daily	5 mg BID to TID then BID and followed by daily dosing before discontinuation	12 months	49

LVEF: left ventricular ejection fraction; mg: milligrams; BID: twice per day; TID: three times per day.

Herein, it is in the context of these studies, we present four patients in our practice with hypotension secondary to left ventricular dysfunction in which we utilized midodrine in a non-fixed, or dose titration manner (Table 1). This permitted for parallel titration of standard of care neurohormonal antagonist therapy that would otherwise not be tolerated. With improved blood pressure gains from midodrine initiation, it allowed us to make marked improvement in systolic function with GDMT.

Case reports

Case 1: A 56-year-old Caucasian male with a history of hypothyroidism, dyslipidemia, hypertension, and chronic systolic heart failure presented to the hospital with complaints of dizziness and lightheadedness. His electrocardiogram (ECG) demonstrated sinus bradycardia with a left anterior hemiblock. His heart rate at home was 45 beats per minute and blood pressure was only 90 mmHg systolic. An echocardiogram demonstrated a left ventricular ejection fraction (LVEF) of 35% with a moderately dilated left ventricle. Consultation with the electrophysiologist was obtained and a dual-chamber internal cardiac defibrillator (ICD) was implanted. He also underwent a cardiac catheterization which showed no atherosclerotic disease. He was able to tolerate a low dose diuretic, ramipril 2.5 mg daily plus carvedilol 3.125 mg by mouth twice daily at discharge. A follow-up echocardiogram in the office showed his LVEF improved to 40%.

He was followed closely by the cardiologist, and 3 years later, he developed low blood pressure of 70/52 mmHg and was symptomatic. His ramipril was discontinued, but he continued to have episodes of hypotension so his carvedilol and losartan were also discontinued 3 months later; his blood pressure and symptoms then stabilized but then 1 week later, the patient developed recurrent lightheadedness with an associated blood pressure of 90/60 mmHg. Midodrine 2.5 mg twice a day (BID) was started with gradual up titration first to three times daily (TID) then in 2.5 mg increments up to a maximum of 10 mg by mouth TID to maintain systolic blood pressure no greater than 100 mmHg. Two years later, he continued on midodrine daily to maintain his blood pressure, and at that time it was decided to attempt to resume his carvedilol 3.125 mg BID while continuing the midodrine. The carvedilol was eventually increased to 6.25 mg BID, and his LVEF improved to 43% several months later so losartan 25 mg daily was then reintroduced. Midodrine was continued and a repeat echocardiogram several months later demonstrated a LVEF of 52% and the midodrine was weaned off. The taper regimen from 10 mg TID proceeded in stepwise fashion first to 5 mg TID, proceeding to BID then daily before discontinuation. This patient today continues on his cardiac medication regimen as described and maintains an ejection fraction (EF) of approximately 58%. In summary, this patient was on midodrine for a duration of approximately 24 months and GDMT was resumed which resulted in an overall improvement in his LVEF.

Case 2: A 58-year-old African American female presented with ventricular fibrillation and was successfully defibrillated with no neurological sequelae. She had a history of hypertension and obesity but no cardiac history. Her subsequent ECG showed a left bundle branch block for which she

then received a cardiac catheterization which determined she had no significant coronary artery disease but an EF of 18%. Prior to discharge, the patient had an ICD/cardiac resynchronization therapy device placed and she was then discharged home on furosemide, carvedilol, and losartan. She was rehospitalized 2 weeks later due to hypotension, and her carvedilol and losartan were discontinued. After discharge, we started the patient on midodrine 2.5 mg BID and increased first to TID dosing followed by an increase to 5 mg three times per day. We gradually restarted her carvedilol and losartan which we were able to titrate up as she continued on her diuretic. After approximately 2 months, the midodrine was weaned off at her 5 mg TID dose without taper. An echocardiogram was performed at a subsequent visit which showed her LVEF had increased to 28%. Two years later, she was stable and a new combination drug, sacubitril-valsartan, became available which we initiated so her losartan was discontinued. Her current medication regimen is carvedilol 25 mg BID, sacubitril-valsartan 49/51 mg BID, and furosemide 40 mg only as needed. Her most recent EF on this medication regimen was 53% with no symptoms of heart failure and is employed full-time. In summary, after only 2 months of midodrine therapy, we were able to restart her GDMT for heart failure and she had a substantial increase in her LVEF over time.

Case 3: A 61-year-old Caucasian female with a history of hypertension was referred to our cardiology clinic because she was noted to have a sinus rhythm with a left bundle branch block on a screening ECG in the absence of cardiac symptoms. Her echocardiogram showed her LVEF was 48% and a nuclear scan was negative for myocardial ischemia. Eight years later, she presented to the emergency department with submassive and multiple pulmonary emboli causing low blood pressure. She also had extensive deep vein thrombosis of the right leg and urgently received a thrombolytic agent. Her rhythm at the time was atrial fibrillation with a left bundle branch block. An echocardiogram during the admission showed her LVEF to be 30% and she remained in atrial fibrillation for which she was started on amiodarone. While hospitalized, her chest x-ray revealed radiographic features of congestive heart failure and her blood pressure remained low requiring an intravenous vasopressor. After several days, we started her on 2.5 mg BID of midodrine with gradual up titration first to TID then to 5 mg TID at which time we were able to wean her off the vasopressor. At that same time, we attempted to start small doses of carvedilol which she could not tolerate. We finally discharged her home a week later on apixaban, losartan 25 mg daily, metoprolol succinate 25 mg daily, midodrine 5 mg TID, and spironolactone 25 mg daily. A week later at her follow-up appointment, we changed her losartan to sacubitril-valsartan 24/26 BID. One month later, we were able to discontinue the midodrine at 5 mg TID without any further exacerbation of her heart failure symptoms. She had a recent cardiac catheterization which showed normal coronaries and an EF of 40%.

Case 4: A 57-year-old Hispanic female with a history of chronic systolic heart failure and a LVEF of 58% presented to the hospital for acute on chronic systolic heart failure secondary to a non-ST-segment elevation myocardial infarction. She also had a history of insulin-independent diabetes, hypertension, dyslipidemia, and tobacco use disorder. Her cardiac catheterization showed severe coronary artery disease and an aneurysm of 5 centimeters involving the ascending and abdominal aorta with moderate to severe aortic regurgitation. She was discharged and referred to a cardiovascular surgeon and 1 month later, underwent an aortic root replacement, an aortic valve replacement, reimplantation of the coronary buttons, four vessel coronary bypass grafting, along with a dual-chamber permanent pacemaker. Just prior to discharge, her echocardiogram showed a LVEF of 31%, mild LV hypokinesis, and her mechanical aortic valve was functioning normally. Several weeks later, the patient received an abdominal aortic aneurysm repair. The following 2 years, the patient had multiple admissions to the hospital for heart failure and poor blood sugar control. Her blood pressure was low and it made treating her heart failure with GDMT difficult. We initiated midodrine at 5 mg BID followed by an increase to TID dosing before we were able to start carvedilol 6.25 mg and sacubitril-valsartan 25/26 both twice daily as well as spironolactone 25 mg daily. Over the next year, her heart failure improved, and we were able to wean the 5 mg TID of midodrine to BID before switching to once daily dosing then discontinuation. She has had no further admissions to the hospital for heart failure for the past 6 months, and her most recent LVEF was 49%.

Discussion

Hypotension in the setting of heart failure with reduced EF is difficult to treat as the neurohormonal antagonism in GDMT would otherwise worsen underlying poor vascular tone. Midodrine is an alpha 1 adrenergic agonist which initiates a cascade of cellular mediators leading to smooth muscle constriction increasing peripheral resistance. As such, this is one predominant reason it is used in the treatment of symptomatic OH, though recent literature suggests minimal and low-quality evidence to support midodrine use for this indication.[8] The weak vasopressor activity of midodrine is further highlighted by conflicting studies on efficacy to decrease time on vasopressors in ICU patients.[3,4,9,10] Important to note, however, is the concept of dose titration as illustrated by Riker and Gagnon[14] showing a vast majority of these studies were fixed-dose studies, in contrast to titration studies which showed reduction of intravenous vasopressor days among ICU patients. Beyond the peripheral vasoconstrictive effects, there has been emerging evidence to suggest other pharmacological benefits for use of alpha-1 agonists in the

context of heart failure—namely the counter-regulatory role of agents such as midodrine in the reversal of maladaptive cardiac remodeling through direct agonism of alpha 1a subtype adrenergic receptors which are upregulated in the setting of high beta-adrenergic stimulation triggered by declining LVEF.[11] The adaptive and cardioprotective role of alpha 1a subtype receptors is further highlighted during the Antihypertension and Lipid-Lowering Treatment to Prevent Heart Attack Trial also known as the ALLHAT trial showing the use of alpha1-blocker, doxazosin, resulted in an incidence of heart failure twice as high than comparative groups.[15] Collectively, the question of whether the improvement in EF among patients presented in this case series would have occurred in the absence of midodrine is difficult to say. The clinical improvement observed in our case series suggests a potential role of midodrine beyond peripheral vasoconstriction, but also as a key regulator in cell survival pathways and ischemic preconditioning as highlighted by Zhang et al.[11]

In our case series, we demonstrate the prospective therapeutic role of midodrine, an alpha1 agonist with alpha 1a subtype activity, in the arsenal of pharmacotherapeutic agents available to the non-ischemic heart failure population. In all but one case, we initiated a dose of 2.5 mg BID with gradual up titration in 2.5 mg intervals to achieve a conservative systolic blood pressure of 100 mmHg. Utilizing midodrine, we were able to maintain normotensive states among our patients which allowed us to initiate GDMT such as beta blockers, angiotensin receptor-neprilysin inhibitors, ace inhibitors/angiotensin receptor blockers, and/or spironolactone, to reverse cardiac remodeling. Upon LV function and EF improvement, midodrine would then be appropriately discontinued. In this way, midodrine serves as a bridge to the resumption of standard of care medications, and our four cases illustrate this approach can be done successfully. All of the patients' echocardiograms demonstrated normal LV thickness indicating there was a potential for improvement once they could tolerate GDMT. We believe the titration-based approach presented in this case series can be successfully applied to similar patients as described. As few studies exist for the use of midodrine in HFrEF patients, we did not have a formalized protocol for escalation and deescalation other than the aforementioned systolic blood pressure target. Future directions will require a larger study group and a more regimented dose titration protocol in both up- and down-titration.

Conclusion

We presented several cases using midodrine, a medication that has been used for over 20 years for OH to improve GDMT in our heart failure patients with refractory hypotension. This medication has been in our armamentarium for several years where we find it useful to improve the overall health, treatment, and quality of life in this population.

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series where no protected health information is disclosed.

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Informed consent

Written informed consent has been obtained from all patients in this case series for their anonymized information to be published in this article.

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