ORIGINAL CLINICAL REPORT

OPEN

Hemodynamic Effects of an Increased Midodrine Dosing Frequency

Shea A. Macielak, PharmD[1]
Nicholas J. Vollmer, PharmD[1]
Natalie A. Haddad, PharmD[1]
Christoph G. S. Nabzdyk, MD[2]
Scott D. Nei, PharmD[1]

OBJECTIVES: In practice, midodrine has been used to reduce IV vasopressor requirements and decrease ICU length of stay. However, recent publications have failed to show clinical success when midodrine was administered every 8 hours. One possible reason for the lack of clinical efficacy at this dosing interval may be the pharmacokinetic properties of midodrine that support a more frequent dosing interval. Here, we report our institutional experience with midodrine at a dosing frequency of every 6 hours.

DESIGN: Single, quaternary academic medical center, retrospective, descriptive study.

SETTING: Floor and ICU patients admitted to Mayo Clinic, Rochester, from May 7, 2018, to September 30, 2020.

PATIENTS: Adult patients with an order for midodrine with a dosing frequency of "every 6 hours" or "four times daily" were eligible for inclusion.

INTERVENTIONS: No intervention performed. All data were abstracted retrospectively from the electronic medical record.

MEASUREMENTS AND MAIN RESULTS: Forty-four unique patients were identified that met inclusion criteria. Patients were an average of 65 years and 63.6% were male. The individual doses of midodrine ranged from 5 to 20 mg. Twenty-three patients (52.3%) were receiving IV vasopressors at the time midodrine was ordered every 6 hours. Vasopressor requirements decreased from an average of 0.10 norepinephrine equivalents 24 hours prior to the every 6-hour order to 0.05 norepinephrine equivalents 24 hours after an order for midodrine every 6 hour was placed.

CONCLUSIONS: Increasing the dosing frequency of midodrine to every 6 hours may optimize its pharmacokinetic profile without compromising safety. This midodrine dosing frequency should be prospectively evaluated as a primary strategy for accelerated IV vasopressor wean.

KEY WORDS: hemodynamics; intensive care; midodrine; pharmacokinetics; vasopressors

Even at low doses, continuous IV vasopressor requirements represent a barrier to discharge from the ICU in most institutions, which could potentially increase a patient's risk for catheter-related infections, antimicrobial resistance, delirium, and ultimately, mortality (1). Additionally, it poses a burden on the healthcare system, especially during periods of high ICU utilization as it is currently the case during the coronavirus disease 2019 pandemic. Although vasopressors carry numerous risks for serious adverse effects, including tachyarrhythmias and ischemia, midodrine has a very favorable side effect profile, with the most common adverse effect reported being bradycardia (2).

DOI: 10.1097/CCE.0000000000000405

Midodrine is a direct acting oral alpha-1 adrenergic agonist that is approved by the U.S. Federal Drug Administration (FDA) for the treatment of symptomatic orthostatic hypotension in the ambulatory setting. Midodrine use has significantly increased within the past decade. In a single-center retrospective review, the number of patients prescribed midodrine in the inpatient setting between 2011 and 2016 had increased by a factor of ~6 (3). Observational studies found that a single dose of 20 mg of midodrine can increase a patient's systolic blood pressure (SBP) by approximately 43 mm Hg 1 hour after administration (4). Midodrine is a prodrug that undergoes enzymatic hydrolysis in the liver and other tissues to its active form, desglymidodrine. This process takes approximately 30 minutes, with desglymidodrine reaching peak concentrations within 1–2 hours (2). Considering that the half-life of the active moiety of midodrine is 3–4 hours, a therapeutic concentration may not be sustained with commonly used extended dosing intervals of every 8–12 hours. Despite a lack of FDA approval for alternative indications, off-label inpatient use of midodrine has become more common, particularly in the ICU as a means to reduce vasopressor needs and ICU length of stay (3).

Previous pharmacokinetic studies have found that SBP typically returns to baseline 6 hours after midodrine administration (4). Despite this established pharmacokinetic data and midodrine's short half-life, the majority of observational studies used a dosing regimen of 5–20 mg every 8 hours, with few studies adopting a more frequent dosing regimen (5, 6). Observational and retrospective studies have found that midodrine use was associated with an accelerated vasopressor decline and reduced ICU length of stay with the every 8-hour dosing frequency (5, 6). In contrast, some observational studies and a recent randomized-controlled study have failed to replicate this benefit (7–9). It is conceivable that the low-frequency dosing strategies (every 8 hr or less frequent) may have contributed to the negative trial results (9). Here, we report our institution's experience of a high midodrine dosing frequency (every 6 hr) and its impact on the patients' hemodynamics.

MATERIALS AND METHODS

This single-center, retrospective study describes patients who had an order for midodrine at a frequency of "four times daily" or "every 6 hours," between May 7, 2018, and September 30, 2020. Patients were identified and data were collected from the electronic medical record. Patients who were incarcerated, pregnant, were less than 18 years old, and those with documented refusal of Minnesota research authorization were excluded. This study was approved by the Mayo Clinic Institutional Review Board (IRB) with exempt status (IRB No. 20-010944).

Demographic information including age, sex, laboratory values at the time of the midodrine order, and level of care was abstracted retrospectively from the electronic medical record. Information about the indication, dose, frequency, and duration of the midodrine order was also collected based on retrospective data. Vasopressor doses were collected at 24 and 12 hours prior to when the order was placed for every 6-hour midodrine, at the time the order was placed, and 24 hours after the order was placed. Authors reviewed each case for adverse events during or after midodrine administration. Adverse events were classified as mesenteric ischemia, digital ischemia, or bradycardia (heart rate <50). Vasopressor doses were converted into norepinephrine equivalents (NEE) using the following calculation from the Angiotensin II for the treatment of Vasodilatory Shock-3 trial: NEE = Norepinephrine μg/kg/min + Epinephrine μg/kg/min + (Vasopressin units/min × 2.5) + (Dopamine × 0.0067 μg/kg/min) + (Phenylephrine × 0.1 μg/kg/min) (10). All data were presented with descriptive statistics. Baseline statistics were presented in median and interquartile ranges or percentages. All data were handled using JMP version 14.0 software (SAS Institute Inc., Cary, NC).

RESULTS

Forty-seven unique patients were identified for which an order was placed for midodrine at a frequency of every 6 hours between May 7, 2018, and September 30, 2020. One patient was excluded due to less than 18 years old and two patients were excluded for never receiving midodrine at a true 6-hour interval. Therefore, a total of 44 patients were included in the final analysis. The study population was primarily male (63.6%) and non-Hispanic or Latino (97.7%). The majority of patients were admitted to the ICU (75%), and midodrine was initiated in the ICU in 56.8% of patients. The primary indication for ICU admission was recovery from a surgical intervention (51.5% of patients admitted to the

TABLE 1.
Patient Demographics and Clinical Characteristics

Variable	*n* (%)
Age (yr)	65 (52–72)
Male (sex)	28 (63.6)
Body mass index (kg/m^2)	27.4 (22.9–35.0)
Race (Hispanic or Latino)	1 (2.3)
Serum creatinine (mg/dL)	1.56 (0.85–2.33)
Alanine aminotransferase[a]	21 (12–41)
Aspartate aminotransferase[a]	33 (23–76)
Alkaline phosphatase[a]	111 (68–170)
Admitted to ICU	33 (75.0)
ICU length of stay	12 (5–27)
Outpatient prescription for midodrine prior to admission	18 (40.9)
Mortality	13 (29.5)
Midodrine started in ICU	25 (56.8)
Order for Q8H/tid dosing prior to Q6H/four times daily dosing	32 (72.7)
Duration of Q8H order (d)	2.9 (1.0–8.3)
Duration of Q6H order (d)	2.8 (0.9–6.1)
Midodrine dose titrated off prior to discharge	21 (47.7)
Dose reescalation of midodrine had to occur while tapering or stopping	4 (9.1)
Concurrently on corticosteroids during midodrine administration	19 (43.2)
On anthihypertensives at the time of midodrine order	7 (15.9)
Beta blocker	6 (13.6)
Calcium channel blocker	3 (6.8)
Direct vasodilators	0 (0)
Angiotensin-converting enzyme inhibitor	0 (0)
Angiotensin receptor blocker	0 (0)
Angiotensin receptor-neprilysin inhibitor	0 (0)
Alpha antagonist	0 (0)
Alpha-2 agonist	0 (0)
Adverse effect	1 (2.3)
Bradycardia	0 (0)
Digital ischemia	0 (0)
Mesenteric ischemia	1 (2.3)

Q6H = every 6 hr, Q8H = every 8 hr.

[a]Closest to time of order for every 6 hr.

Details including midodrine dosing and concomitant therapy are also displayed. Results are displayed as number (%) or median (IQR) unless otherwise noted.

ICU). Furthermore, 72.7% of the patients had an order for midodrine administered every 8 hours or tid prior to the order for every 6 hours. Individual midodrine doses ranged from 5 to 20 mg with an average dose of 12 mg every 6 hours. Full baseline patient characteristics are included in **Table 1**.

Interestingly, a total of 18 patients (40.9%) were on midodrine prior to admission with the most common indication being orthostatic hypotension. Home dosing frequencies ranged from bid to four times a day dosing with individual doses between 2.5 and 10 mg. The eight patients receiving four times per day dosing prior to hospitalization had no further escalation of dosing in the hospital setting in regard to milligram dose or frequency. This remained true even if the patient required vasopressors for hemodynamic support.

When considering trends in vasopressor requirements, patients who were on midodrine prior to their hospitalization were excluded from analysis. Twenty-three were on vasopressors in the ICU at the time that midodrine was ordered and were not on midodrine at home. Those that were receiving vasopressors were on an average of 0.1 NEE 24 hours prior to the order for every 6-hour midodrine, 0.1 NEE at the time the every 6-hour order was placed, and 0.06 NEE 24 hours after the order was placed. Vasopressor trends are displayed in **Figure 1**.

Based on retrospective review, only one patient experienced an adverse effect. Mesenteric ischemia was documented for this one patient. However, this was in the setting of multiple vasopressors that were initiated prior to midodrine administration and persistent low cardiac output state. None of the patients experienced digital ischemia or bradycardia, defined as a heart rate less than 50 beats/min. Review of the 13 deaths showed that 11 were transitions to comfort care in the setting of a cancer diagnosis or multisystem organ failure. The two remaining deaths were an arrest in the setting of multisystem organ failures and the other refractory septic shock.

DISCUSSION

This retrospective data from a single academic medical center illustrates that midodrine can be administered every 6 hours without major safety concerns. Furthermore, this midodrine dosing frequency appeared to facilitate IV vasopressor weaning in the majority of patients within 24 hours of order placement in those admitted to the ICU. Only one patient experienced an adverse event, mesenteric ischemia, although this was in the setting of concomitant IV vasopressor therapy and low cardiac output state. No other adverse effects were noted on retrospective review.

Considering that the half-life of the active moiety of midodrine is 3–4 hours, a therapeutic concentration may not be sustained with commonly used extended dosing intervals of every 8 or 12 hours. In fact, these pharmacokinetics data suggest that the optimal dosing interval might be even more frequent than every 6 hours. Identifying this optimal dosing interval could help establish midodrine as a tool to facilitate IV vasopressor weaning and to possibly achieve shorter ICU lengths of stay.

In line with this argument, Riker and Gagnon (11) recently noted the need to assess midodrine efficacy based on a titrated rather than a fixed dosing strategy. In previous studies, midodrine was efficacious in reducing the duration of IV vasopressor use and ICU

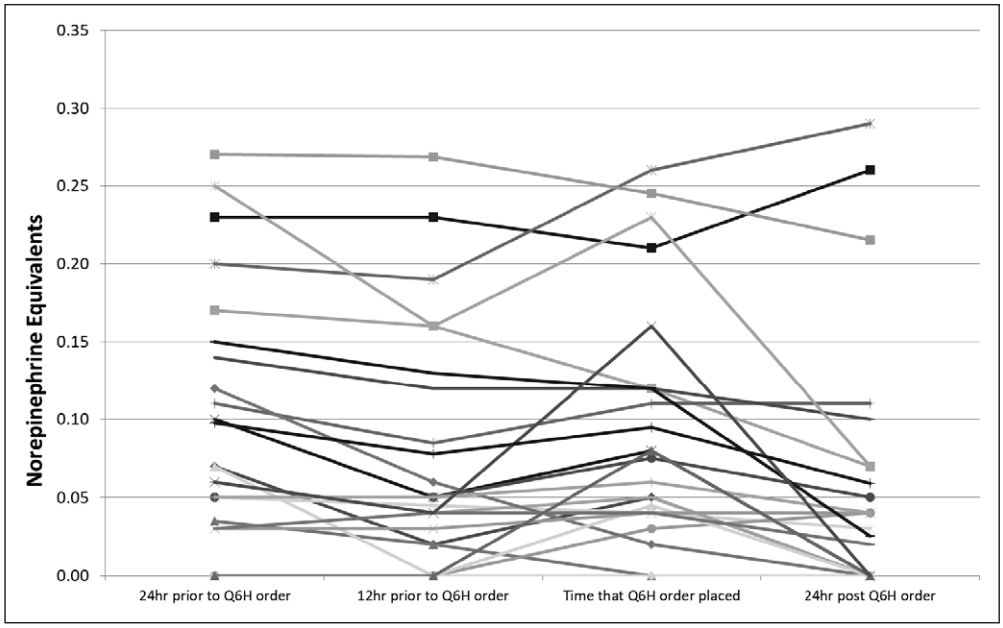

Figure 1. Vasopressor requirements of the 23 patients on IV vasopressors in the immediate time period before and after midodrine was ordered at a frequency of every 6 hr (Q6H), which were not previously on home midodrine. All vasopressors were converted into norepinephrine equivalents.

length of stay when titrated to clinical response (2, 5, 6, 8). This is contrary to the findings of the prospective effect of midodrine versus placebo on time to vasopressor discontinuation in patients with persistent hypotension in the ICU - an international randomised clinical trial, in which midodrine at a fixed dose of 20 mg every 8 hours did not expedite the discontinuation of a single vasopressor compared with placebo (9).

An unexpected finding in this study was a high degree of home midodrine use. Eight of the 18 patients on midodrine prior to hospitalization were already escalated to four times per day dosing regimens in the home setting. From one perspective, this is encouraging in terms of the long-term safety of a more frequent dosing strategy. Contrarily, none of these patients had any further escalation of their dosing strategy in terms of frequency or milligram dosage in the inpatient setting. This may reflect provider hesitation with titrating midodrine most commonly seen dosing regimens, which highlights the importance of further investigation of this topic.

As a retrospective, single-center study, our study has several limitations, which prevent definitive conclusions. Over 70% of the patients included in this study had an order for midodrine at a frequency of every 8 hours prior to escalating to every 6 hours. This cross over limits the feasibility of comparing every 8 hour dosing to every 6 hour but provides basis for future research. Due to the complex nature of the drug therapy regimens in these patients, adjustments and trends in medications other than vasopressors were not assessed, which may have been confounders. This was a heterogeneous group of patients with 25% of the population never being admitted to the ICU. However, the inclusion of these patients offers insight to the spectrum of patients that tolerate every 6-hour dosing. The included patients also had a variety of indications for midodrine use, which limits the ability to draw conclusions for one specific indication. Despite these limitations, this investigation supports the potential for alternative dosing modalities of midodrine to facilitate vasopressor weaning in the ICU.

CONCLUSIONS

Increasing the dosing frequency of midodrine to every 6 hours may optimize its pharmacokinetic profile without compromising safety. There is a need to evaluate prospectively this increased midodrine dosing frequency as a strategy to wean IV vasopressors in future studies.

1 *Department of Pharmacy, Mayo Clinic, Rochester, MN.*

2 *Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN.*

The authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: macielak.shea@mayo.edu

REFERENCES

1. Mazzeffi M, Gammie J, Taylor B, et al: Healthcare-associated infections in cardiac surgery patients with prolonged intensive care unit stay. *Ann Thorac Surg* 2017; 103:1165–1170
2. *ProAmatine (midodrine tablets)* [package insert]. Lexington, MA, Shire US, 2017.
3. Rizvi MS, Trivedi V, Nasim F, et al: Trends in use of midodrine in the ICU: A single-center retrospective case series. *Crit Care Med* 2018; 46:e628–e633
4. Wright RA, Kaufmann HC, Perera R, et al: A double-blind, dose-response study of midodrine in neurogenic orthostatic hypotension. *Neurology* 1998; 51:120–124
5. Levine AR, Meyer MJ, Bittner EA, et al: Oral midodrine treatment accelerates the liberation of intensive care unit patients from intravenous vasopressor infusions. *J Crit Care* 2013; 28:756–762
6. Whitson MR, Mo E, Nabi T, et al: Feasibility, utility, and safety of midodrine during recovery phase from septic shock. *Chest* 2016; 149:1380–1383
7. Roach E, Adie S, Gowan M, et al: 200: Impact of oral midodrine on duration of intravenous vasopressor therapy. *Crit Care Med* 2018; 46:82
8. Poveromo LB, Michalets EL, Sutherland SE: Midodrine for the weaning of vasopressor infusions. *J Clin Pharm Ther* 2016; 41:260–265
9. Santer P, Anstey MH, Patrocínio MD, et al; MIDAS Study Group: Effect of midodrine versus placebo on time to vasopressor discontinuation in patients with persistent hypotension in the intensive care unit (MIDAS): An international randomised clinical trial. *Intensive Care Med* 2020; 46:1884–1893
10. Khanna A, English SW, Wang XS, et al: Angiotensin II for the treatment of vasodilatory shock. *N Engl J Med* 2017; 377:419–430
11. Riker RR, Gagnon DJ: Midodrine administration during critical illness: Fixed-dose or titrate to response? *Intensive Care Med* 2021; 47:249–251