Under Pressure to Stop Pressors: What is the Role of Oral Vasoactive Medications in the ICU?

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Pharmacy Grand Rounds
October 4, 2016
Presentation Objectives

• Review the pharmacology of oral vasoactive medications

• Describe the potential role of oral vasoactive medications in the intensive care unit

• Identify patient specific factors warranting the safe use of oral vasoactive medications in the intensive care unit
Septic shock

Hypovolemia

Endocrine emergencies

Idiosyncratic reactions from medications

Cardiac dysfunction

Positive pressure ventilation

Complications of Prolonged ICU stay

- Delirium
- ICU acquired antimicrobial-resistant bacterial infections
- Central line infections
- Immobilization
- Cost

ICU: intensive care unit
Off-Label Uses of Midodrine in the ICU

- Intradialytic hypotension
- Cirrhosis and ascites
- Hepatorenal syndrome
- Vasovagal syndrome

POTS: postural orthostatic tachycardia syndrome

Midodrine and the FDA

1996: Approved as orphan drug

2010: FDA continued to make available

“…would be incapacitated by the conditions for which they take midodrine if the drug were withdrawn…”

2012: Further clinical trials to be completed
Midodrine

Arterioles

Veins

Direct stimulation of α1

Systemic vascular resistance

Midodrine

- **PKPD**:
  - Pharmacokinetics
  - Pharmacodynamics

- **SBP**: supine blood pressure

- **Midodrine**: 20mg (n=22), 10mg (n=23), 2.5mg (n=24)

- **Placebo**: (n=23)

**Graph Details**:
- **Peak**:
  - Midodrine 20mg: 1-2 hours
  - Midodrine 10mg: 1-2 hours
  - Midodrine 2.5mg: 3-4 hours

- **Bioavailability**:
  - Midodrine 20mg: 93%
  - Midodrine 10mg: 80%
  - Midodrine 2.5mg: 90%

- **Half life**:
  - Midodrine 20mg: 3-4 hours
  - Midodrine 10mg: 4-5 hours
  - Midodrine 2.5mg: 2-3 hours

- **Time (hours)**: 0-6

- **Standing SBP**: 80-140

References:
Midodrine

- Supine hypertension
- Compensatory bradycardia
- Piloerection
- Shivering
- Paresthesias
- Urinary retention

Black Box Warning

- Marked elevation of supine BP
- Use only in patients whose lives are “considerably impaired despite standard clinical care”
By what mechanism does midodrine increase systemic vascular resistance?

- β1- and β2-agonism
- α1-agonism
- α1- and β1-agonism
- Unknown mechanism of action
### Comparing Vasopressors with Midodrine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Receptor affinity</th>
<th>Dose</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>α1 &gt; β1</td>
<td>0.05-1 mcg/kg/min</td>
<td>Tachycardia, peripheral/GI ischemia</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>β1 &gt; α1</td>
<td>0.05-0.5 mcg/kg/min</td>
<td>Tachycardia, peripheral/GI ischemia</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>α1</td>
<td>0.5-5 mcg/kg/min</td>
<td>Tachyphylaxis</td>
</tr>
<tr>
<td>Dopamine</td>
<td>DA, β1, α1</td>
<td>5-20 mcg/kg/min</td>
<td>Tachycardia, arrhythmias</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>V1</td>
<td>0.03-0.04 units/min</td>
<td>Cardiac/mesenteric ischemia, skin lesions</td>
</tr>
<tr>
<td>Midodrine</td>
<td>α1</td>
<td>???</td>
<td>Supine hypertension</td>
</tr>
</tbody>
</table>

GI: gastrointestinal

In the literature, midodrine has been shown to:

• Reduce the duration of IV vasopressors during the recovery phase from septic shock
• Reduce IV vasopressor requirements in a surgical ICU
• Replace IV vasopressors in a medical ICU
• A and B
• All of the above
## Midodrine Use in the SICU

Oral midodrine treatment accelerates the liberation of ICU patients from IV vasopressor infusions

<table>
<thead>
<tr>
<th>Design</th>
<th>Single center, prospective, single arm, observational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>Magnitude of change in IV vasopressor rate</td>
</tr>
</tbody>
</table>

**Patients**

**Inclusion:**
- SICU patients >18 years old
- Requiring persistent IV vasopressors

**Exclusion:**
- Less than three doses of midodrine
- Hypotensive secondary to hypovolemia or adrenal insufficiency
- History of orthostatic hypotension
Midodrine Use in the SICU

<table>
<thead>
<tr>
<th>Demographics</th>
<th>n = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean, SD)</td>
<td>65 ± 14</td>
</tr>
<tr>
<td>Vasopressor days pre-midodrine, days (IQR)</td>
<td>3 (2-6)</td>
</tr>
<tr>
<td>PE equivalent pre-midodrine, mcg/min (mean, SD)</td>
<td>41 ± 33.4</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL (mean, SD)</td>
<td>0.74 ± 0.28</td>
</tr>
<tr>
<td>Surgical service, n</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>4</td>
</tr>
<tr>
<td>General</td>
<td>3</td>
</tr>
<tr>
<td>Orthopedic</td>
<td>4</td>
</tr>
<tr>
<td>Thoracic</td>
<td>8</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>1</td>
</tr>
</tbody>
</table>
Midodrine Use in the SICU

- Vasopressor discontinuation
  - Median time from midodrine initiation: 17 hours (IQR: 7-38.4)
  - 14 patients off vasopressors within 24 hours

- Midodrine modal dose
  - 20mg (range, 5-20mg) TID

<table>
<thead>
<tr>
<th>PE equivalents rate change, mcg/kg/min (mean, SD)</th>
<th>Before midodrine</th>
<th>After four doses of midodrine</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.006 ± 0.014</td>
<td>-0.22 ± 0.025</td>
<td>0.012</td>
<td></td>
</tr>
</tbody>
</table>

Midodrine Use in the SICU

- Limited population
- Difficult to identify the causes of hypotension
  - Changes in total body fluid balance, heart rate, MAP and WBC did not correlate with changes in IV vasopressor rate
- Potential for bias is increased by single center and observational design
- Optimal dose unknown
## Midodrine During the Recovery Phase of Septic Shock

**Feasibility, utility and safety of midodrine during recovery phase from septic shock**

<table>
<thead>
<tr>
<th>Design</th>
<th>Single center, two-arm, observational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoints</td>
<td>Duration of IV vasopressor administration and ICU LOS</td>
</tr>
<tr>
<td><strong>Inclusion:</strong></td>
<td>Clinically stable MICU patients</td>
</tr>
<tr>
<td></td>
<td>&gt;18 years old</td>
</tr>
<tr>
<td></td>
<td>Diagnosis of septic shock</td>
</tr>
<tr>
<td></td>
<td>Requiring persistent IV vasopressors</td>
</tr>
<tr>
<td><strong>Exclusion:</strong></td>
<td>Unspecified</td>
</tr>
</tbody>
</table>

**LOS:** length of stay

## Midodrine During the Recovery Phase of Septic Shock

<table>
<thead>
<tr>
<th>Demographics</th>
<th>IV vasopressor only (n = 140)</th>
<th>IV vasopressor with midodrine (n = 135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>65 ± 19</td>
<td>69.3 ± 16</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>79 (56%)</td>
<td>64 (47%)</td>
</tr>
<tr>
<td>NE dose upon midodrine initiation, mcg/kg/min (mean, SD)</td>
<td>-</td>
<td>0.09 ± 0.09</td>
</tr>
<tr>
<td>PE dose upon midodrine initiation, mcg/kg/min (mean, SD)</td>
<td>-</td>
<td>1.05 ± 0.77</td>
</tr>
<tr>
<td>Infectious source, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>58 (41.4%)</td>
<td>52 (38.5%)</td>
</tr>
<tr>
<td>Urinary</td>
<td>58 (41.4%)</td>
<td>54 (40%)</td>
</tr>
<tr>
<td>Abdominal</td>
<td>10 (7.1%)</td>
<td>12 (8.9%)</td>
</tr>
</tbody>
</table>

SD: standard deviation

Midodrine During the Recovery Phase of Septic Shock

- **Midodrine dose**
  - Starting: 10mg every eight hours
  - Maximum: $18.7 \pm 9.6$ every eight hours
- **Midodrine discontinued inpatient in 87% of patients**
- **Average duration of midodrine: 6.15 days**

<table>
<thead>
<tr>
<th>Variable</th>
<th>IV vasopressor only (n=140)</th>
<th>IV vasopressor + midodrine (n=135)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV vasopressor duration (days)</td>
<td>3.8</td>
<td>2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>9.4 ± 6.7</td>
<td>7.5 ± 5.9</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Midodrine During the Recovery Phase of Septic Shock

- Decisions were not protocol driven
  - Tapering schedule unknown
  - Stable doses vs. decreasing doses of IV vasopressors?
- Potential for bias is increased by single center and observational design
### Ongoing Clinical Trial

**Midodrine for the treatment of refractory hypotension in patients otherwise ready for discharge from the ICU**

<table>
<thead>
<tr>
<th>Design</th>
<th>Multicenter, double blind, randomized, controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>Time until discontinuation of IV vasopressors after initiation of midodrine</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td></td>
</tr>
<tr>
<td>Inclusion:</td>
<td></td>
</tr>
<tr>
<td>- SICU patients</td>
<td></td>
</tr>
<tr>
<td>- &gt;18 years</td>
<td></td>
</tr>
<tr>
<td>- Requiring persistent IV vasopressors</td>
<td></td>
</tr>
<tr>
<td>Exclusion:</td>
<td></td>
</tr>
<tr>
<td>- Inadequate tissue oxygenation, liver failure, hypovolemic shock</td>
<td></td>
</tr>
<tr>
<td>- Hypotension due to adrenal insufficiency</td>
<td></td>
</tr>
<tr>
<td>- Recent ACEi or ARB use</td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>Midodrine 20mg every eight hours or placebo</td>
</tr>
</tbody>
</table>
In the literature, midodrine has been shown to:

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- All of the above
Midodrine Dosing Pearls

- Recommended to dose every 8 hours
- Titrate up by 10mg per dose per day
- Renally eliminated
- Close monitoring of BP response

BP: blood pressure
Midodrine Dosing Pearls

Free of vasopressor for ≥24 hours

Decrease by 5-10mg per dose per day

Weigh risk of “bouncing back” to ICU

Average duration of 6 days

Not continued as an outpatient

Other Oral Vasoactive Medications

Pseudoephedrine and Droxidopa
Pseudoephedrine

- α1- and β1-adrenergic agonist
- Readily absorbed in the GI tract
  - Onset: 15-30 minutes
  - Duration: 4-6 hours
- Inexpensive
Pseudoephedrine

• Autonomic dysfunction
  • Decreased ability of postganglionic sympathetic neurons to release NE

• Causes
  • Idiopathic, neurogenic shock, spinal cord injury, septic shock

• Difficult to wean from vasopressors

**Pseudoephedrine: A Case Report**

- 77 year old woman requiring 0.4 mcg/kg/min of NE
- Unsuccessful weaning attempts
- Pharmacist consulted for an oral α-adrenergic agonist recommendation
- Pseudoephedrine 60mg every eight hours initiated
- Pseudoephedrine dosage adjustment to 60mg every six hours
- Complete cessation of NE, facilitating ICU discharge

Pseudoephedrine

- Limited data exists for its use as an oral vasoactive agent
- Adverse effects can be serious

- Rapid weaning may be unrealistic

Insomnia  Anxiety  HTN  Arrhythmias  MI  Death

MI: myocardial infarction

Droxidopa

- α1- and β1-adrenergic agonist
- Neurogenic orthostatic hypotension
- Safety
  - Black Box Warning for supine hypertension
- Expensive
- No data
Cost Per 100 Tablets

Midodrine
• 2.5mg: $120
• 5mg: $242
• 10mg: $483

Pseudoephedrine
• 30mg: $3
• 60mg: $5

Droxidopa
• 100mg: $2493
• 200mg: $4986
• 300mg: $7480
An elderly male is admitted to the ICU with sepsis due to pneumonia. By ICU day three, he is dramatically improved but is having difficulty weaning off pressors and continues to require NE @ 0.03 mcg/kg/min. What is the best approach?

- Fluid resuscitate with 30mL/kg in attempt to wean off norepinephrine
- Start droxidopa 100mg every eight hours
- Start midodrine 5mg every eight hours
- Start midodrine 10mg three times daily
Candiates and Starting Doses for Oral Vasoactive Agents

- **Midodrine**
  - Post-surgery
    - 5-10mg every eight hours
  - Septic shock

- **Pseudoephedrine**
  - No recommendation for use can be made
  - 30-60mg every six hours

- **Droxidopa**
  - No recommendation for use can be made

References:

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Avoid Oral Vasoactive Medications if…

- Clinically unstable
  - Requiring increasing doses of vasopressors
- Hypotension due to reversible causes
Conclusion

• Midodrine is a potential oral option for the treatment of refractory hypotension in the ICU
  • Midodrine may reduce ICU LOS and potentially avoid additional complications

• Data from randomized clinical trials are needed to further assess the efficacy and safety of pseudoephedrine and droxidopa for use in the ICU
Questions & Discussion

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