Norepinephrine versus Terlipressin for the Treatment of Hepatorenal Syndrome

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Objectives
1. Describe the pathophysiology of hepatorenal syndrome
2. List the current therapies available for the treatment of hepatorenal syndrome (HRS)
3. Summarize the mechanism of action and adverse effects of pharmacological agents used for the treatment of HRS
4. Summarize the clinical literature providing the evidence for the use of norepinephrine versus terlipressin for the treatment of HRS

Definitions of HRS
- FUNCTIONAL form of acute kidney injury (AKI) that occurs in patients with advanced cirrhosis or fulminant liver failure

<table>
<thead>
<tr>
<th>Type 1 HRS</th>
<th>Scr Increase</th>
<th>Precipitating Event</th>
<th>History of Diuretic-Resistant Ascites</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>+</td>
<td>+/-</td>
<td></td>
<td>10%</td>
</tr>
</tbody>
</table>

Type 1 HRS – Scr increase to a level greater than 2.5 mg/dL in less than 2 weeks
Type 2 HRS – gradual increase in Scr to greater than 1.5 mg/dL

Pathophysiology of HRS
- Disease progression
- Severe portal hypertension
- Bacterial translocation
- Severe splanchnic arterial vasodilatation

Disclosure
- I have no conflicts of interest to disclose

Patient Case
- JM is a 46 y.o. male with the history of anxiety presents from outside hospital with hematemesis, greater than 1 cup of blood, and found to have alcoholic hepatitis in the setting of chronic cirrhosis
- Lab findings on admission
  - Scr 4.2 (baseline 0.9), Tbili 35.9, AST 80, ALT 151, TP 6.6, alb 2.1, INR 1.84
- Vitals on admission
  - HR 90, BP 133/66, RR 18, Tmax 36.8
- Home medications
  - None
**Pathophysiology of HRS**

- Markedly reduced effective arterial blood volume
- Increased cardiac output and plasma volume insufficient to normalize effective arterial blood volume
- Activation of sodium-retaining and vasoconstrictor systems
- Sodium and water retention and ascites formation
- Further activation of vasoconstrictor systems
- Impairment in cardiac output
- Renal failure

**IAC Diagnosis Criteria**

- Cirrhosis with ascites
- Scr > 1.5 mg/dL
- No improvement of Scr (a decrease in serum < 1.5 mg/dL) after 2 days off diuretics and volume expansion with albumin
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of signs of parenchymal renal disease, as suggested by proteinuria (> 500 mg/dl) or hematuria (> 50 RBC) and/or abnormal renal ultrasound

**Patient Case**

- Lab findings on admission
  - Scr 4.2 (baseline 0.9), Tbil 35.9, AST 80, ALT 151, TP 6.6, alb 2.1, INR 1.84
  - Urinalysis: nitrite (-), LE(-), RBC 3, WBC 1, bacteria – none
- Vitals on admission
  - HR 90, BP 133/66, RR 18, Tmax 36.8
- Home medications
  - None

**Pharmacologic Treatment**

- **Midodrine/Octreotide**
  - **Mechanism of action**
    - Midodrine
      - Act on α1- receptors in vascular smooth muscle cells
    - Octreotide
      - Long-acting somatostatin analog
      - Inhibits glucagon and other vasodilatory peptides in splanchnic and systemic circulations
  - **Dosing recommendations**
    - Midodrine 2.5 to 7.5 mg PO every 8 hours
    - Titrate to 12.5 mg PO every 8 hours
    - Octreotide 100 mcg SC every 8 hours
    - Titrate to 200 mcg SC every 8 hours

- **Norepinephrine**
  - **Mechanism of action**
    - α1-adrenergic receptor agonists
  - **Dosing recommendations**
    - 8-50 mcg/min as continuous IV
    - Goal: 10 mmHg rise of MAP
  - **Duration of therapy**
    - Until serum creatinine decreases <1.5 mg/dL
**Terlipressin**

- Orphan drug – January 2013
- Phase III development drug for the treatment of type 1 HRS
- Mechanism of action
  - Long-acting synthetic vasopressin analogue
  - Binds to V1 and V2 receptors
- Metabolism
  - Exopeptidases release small amounts of lysine vasopressin over a sustained period
  - Pharmacologic $t_{1/2} = 6$ hours
  - Elimination $t_{1/2} = 50$ minutes

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**Terlipressin**

- Dosing recommendations
  - 1mg IV every 4-6 hours
  - Titrate a maximum of 2 mg IV every 4-6 hours after 3 days if there is no response to therapy
  - Goal: Decrease in Scr > 25% of pretreatment values (Scr <1.5 mg/dL)
- Duration of therapy
  - 5-15 days
- Adverse effects

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**Methods**

- Inclusion criteria
  - Decompensated cirrhosis and HRS-1 with Scr > 2.5 mg/dL or CrCl<sub>24</sub> < 20 mL/min
- Exclusion criteria
  - Improvement in renal function after central blood volume expansion
  - History of infection within the past week, excluding SBP
  - History of coronary artery disease, obstructive cardiomyopathy, ventricular arrhythmia, or obliterator arterial disease of the limbs

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**Results**

- 49 patients were enrolled in the trial
- Exclusion
  - 5 patients – renal function improvement after volume expansion
  - 4 patients - sepsis
- Etiology of cirrhosis
  - Alcohol (N = 23); hepatitis B (N = 8); hepatitis C (N = 4); cryptogenic (N = 5)
- Baseline characteristics
  - Mean MELD score: NE = 31.6 Terli = 29.6 $p = 0.318$
  - Mean Scr: NE = 3.3 Terli = 3.0 $p = 0.352$
  - Mean CrCl: NE = 14.7 Terli = 14 $p = 0.675$
  - Mean MAP: NE = 78.2 Terli = 81.4 $p = 0.261$
Results

• Partial response – 7 patients
• Non-responders – 13 patients
• Responders – 20 patients
  • Norepinephrine
    • Median dose 25 (range 8-50) mcg/min
    • Median duration 6.5 (range 4–15) days
  • Terlipressin
    • Median dose 4.0 (range 2.0–8.0) mg/day
    • Median duration 7 (range 4–15) days

Table 1. Effect of Norepinephrine Compared to Terlipressin on Renal Function and MAP in Patients With Type 1 HRS

<table>
<thead>
<tr>
<th></th>
<th>Base Line</th>
<th>P-value</th>
<th>Day 15</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>20</td>
<td>20</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Percent responders</td>
<td>0</td>
<td>0</td>
<td>10(10%)</td>
<td>8(40%)</td>
</tr>
<tr>
<td>Mean Scr, mg/dL</td>
<td>1.0±0.1</td>
<td>1.0±0.1</td>
<td>1.0±0.1</td>
<td>1.2±0.5</td>
</tr>
<tr>
<td>Mean CrCl, mL/min</td>
<td>12.8±5.5</td>
<td>13.9±5.0</td>
<td>12.8±4.2</td>
<td>14.9±27.5</td>
</tr>
<tr>
<td>Mean MAP, mmHg</td>
<td>78.3±5.3</td>
<td>84.1±11.3</td>
<td>93.1±8.8</td>
<td>93.1±11.6</td>
</tr>
</tbody>
</table>

NE – Norepinephrine, Terli – Terlipressin, Scr – serum creatinine, MAP – mean arterial pressure, CrCl – creatinine clearance

Figure 3. Cumulative probability of survival

Results

• Cost Calculation
  • Terlipressin 6 mg/day for 15 days for the treatment of HRS-1 - $2,500
  • Noradrenaline (16 mcg/min/day) - $750

• Side Effects
  • ST depression of > 0.1 mV on ECG - 1pt/group
  • Abdominal cramps – 4 pt – terlipressin
  • Ventricular ectopics – 2 pt – norepinephrine group

Conclusion

• Norepinephrine may be an effective, safe, and less costly alternative
• Despite the marked improvement in renal function after vasoconstrictor therapy, the GFR did not reach normal levels in any of the patients

Pharmacist Role in HRS Screening

• Review patient medication profile
• Discontinue diuretic therapy or any other nephrotoxic medications
• Advise primary care team to initiate volume expansion
  • Failure of Scr improvement by ~ 10% from baseline signifies possible HRS
Pharmacist Role in HRS Treatment

- Ensure daily administration of albumin 25% IV
  - ~25g IV (NOT 100g)
- Recommend loop diuretics
- Start vasopressor therapy
  - IV norepinephrine (max 30 mcg/min)
  - Terlipressin 1 mg (2 mg max) IV every 4-6 hours
  - Midodrine 2.5-15 PO mg TID + octreotide 100-200 mcg SC BID

Pharmacist Role in HRS Prevention

- Diuretic therapy
  - Spironolactone 100 mg/Furosemide 40 mg
- Ensure 8g/L of removed ascitic fluid IV after LVP
- Prophylactic antibiotics
  - Variceal hemorrhage
    - Ceftriaxone 1000 mg IV Daily (5 to 7 days)
    - Long term use: patients with previous SBP
      - Norfloxacin 400 mg Daily
      - Ciprofloxacin 750 mg ONCE week
- SBP treatment
  - Ceftriaxone 1000 mg IV every 24 hours
  - Ciprofloxacin 400 mg IV every 12 hours

Patient Case

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References

- Sharma P. An Open Label, Pilot, Randomized Controlled Trial of Noradrenaline Versus Terlipressin in the Treatment of Type 1 Hepatorenal Syndrome and Predictors of Response. Am J Gastroenterol 2008;103:1689-1697