Society of Critical Care Medicine
Texas Chapter
7th Annual Symposium
“Less is More in Critical Care”

October 20, 2018
Catecholamine-Sparing Strategies

Tamara Reiter, Pharm.D., BCCCP
Clinical Pharmacy Specialist—Critical Care
PGY2 Critical Care Residency Program Director
Methodist Dallas Medical Center
Dallas, TX
Disclosures

- La Jolla Pharmaceutical Company
  - Advisory Board meeting attendance
Objectives

• Discuss the utilization of angiotensin II in refractory vasodilatory shock
• Examine the evolving evidence for novel V1a receptor agonist therapies in refractory septic shock
Overview

• Introduction
  ▫ Review catecholamine vasopressors
  ▫ Rationale for catecholamine-sparing strategies
• Angiotensin II
• V1a Receptor Agonists
• Conclusions
Vasopressors

• First isolated ~ 1900
• Catecholamines
  ▫ Norepinephrine
  ▫ Epinephrine
  ▫ Dopamine
• Non-catecholamines
  ▫ Phenylephrine
  ▫ Vasopressin/terlipressin
  ▫ Angiotensin II (AT2)

Adverse Effects of Catecholamines

- Arrhythmias
- Ischemia
- Increased myocardial O2 demand
- Hyperglycemia
- Decreased cardiac output
- Inflammation
- Immunosuppression
- Increased mortality??
Angiotensin II
Renin-angiotensin-aldosterone system

By Soupvector - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=66583851
Angiotensin II

- Has been used in humans since 1940s for a variety of disease states
- Recent review of ~1100 studies in > 31,000 patients
  - 34 studies demonstrated dose-response relationship on BP (only 2 studies in hypotensive patients)
  - Cirrhosis w/ ascites → less sensitive to pressor effects; natriuresis and diuresis
  - Pregnancy → progressive resistance to pressor effects
- Safety
  - Potential to exacerbate LV failure in acute CHF
  - Potential to cause asthma exacerbation

BP = blood pressure; LV = left ventricular; CHF = congestive heart failure
ATHOS-3

- Phase III trial evaluating AT2 for severe vasodilatory shock
  - Randomized, double-blind, multicenter, placebo-controlled; May 2015-January 2017
  - N = 321
  - Purpose: to determine effectiveness of AT2 for vasodilatory shock resistant to high-dose vasopressors
  - Primary Outcome: MAP response 3 hours after start of infusion

MAP = mean arterial pressure
# ATHOS-3 Results

| Outcome                              | AT2  
<table>
<thead>
<tr>
<th></th>
<th>(N=163) (%)</th>
<th>Placebo (N=158) (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP response at hour 3</td>
<td>114* (70)</td>
<td>37 (23)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean change in SOFA score</td>
<td>1.05±5.5</td>
<td>1.04±5.34</td>
<td>0.49</td>
</tr>
<tr>
<td>7-day all cause mortality</td>
<td>47 (29)</td>
<td>55 (35)</td>
<td>0.22</td>
</tr>
<tr>
<td>28-day all cause mortality</td>
<td>75 (46)</td>
<td>85 (54)</td>
<td>0.12</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>99 (61)</td>
<td>106 (67)</td>
<td>-</td>
</tr>
</tbody>
</table>

*79/114 (69%) were “super-responders”

## Subgroup Analyses

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>Day 28 Mortality (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(AT2 = 163; placebo = 158)</td>
<td></td>
<td>(AT2 vs. placebo)</td>
<td></td>
</tr>
<tr>
<td>“Super-responders”</td>
<td>79 vs. 84</td>
<td>32.9 vs. 58.6</td>
<td>0.0007</td>
</tr>
<tr>
<td>N/A (placebo)</td>
<td></td>
<td>53.9</td>
<td></td>
</tr>
<tr>
<td>APACHE II &gt; 30</td>
<td>58 vs. 65</td>
<td>51.8 vs. 70.8</td>
<td>0.037</td>
</tr>
<tr>
<td>AKI on RRT</td>
<td>45 vs. 60</td>
<td>53 vs. 30</td>
<td>0.012</td>
</tr>
<tr>
<td>MAP &lt; 65</td>
<td>52 vs. 50</td>
<td>54.2 vs. 70.4</td>
<td>0.10</td>
</tr>
<tr>
<td>ARDS*</td>
<td>122 vs. 121</td>
<td>48 vs. 57</td>
<td>NS</td>
</tr>
<tr>
<td>AT1/AT2 ≥ 1.63**</td>
<td>68 vs. 72</td>
<td>HR 0.64</td>
<td>0.047</td>
</tr>
<tr>
<td>(AT2 = 142; placebo = 139)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Defined by baseline PaO2/FiO2 < 300

**Signifies relatively low AT2 state

---

## Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>AT2 (N=163)</th>
<th>Placebo (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>142</td>
<td>145</td>
</tr>
<tr>
<td>Any leading to discontinuation</td>
<td>23</td>
<td>34</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Peripheral ischemia</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Thrombotic events</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Delirium</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Acidosis</td>
<td>9</td>
<td>1</td>
</tr>
</tbody>
</table>

ATHOS-3 Critiques

- Manufacturer involved in all aspects of trial
- Dosing protocol
- No details provided regarding other care provided (~90% septic shock)
- Inclusion criteria
  - 25 mL/kg fluid resuscitation
  - ScvO2 & CVP or CI used to define high-output shock
- Goal MAP 75 mmHg
- No clinically meaningful short-term outcomes reported
  - Lactate clearance, urine output

SCVO2 = central venous oxygen saturation; CVP = central venous pressure; CI = cardiac index
AT2—The Good, The Bad, and The Ugly

• Good
  ▫ Effective vasopressor
  ▫ Catecholamine-sparing
  ▫ May provide benefit in certain populations

• Bad
  ▫ Very limited published data in septic shock
  ▫ Concerning ADEs

• Ugly
  ▫ AWP $1800 per vial

ADE = adverse drug event; AWP = average wholesale price
Unanswered Questions

- Is the catecholamine-sparing effect enough?
- What is the effect on short-term outcomes?
- Are there long-term adverse effects?
- Who are the ideal patients?
- What is the ideal starting dose?
Conclusions

- AT2 is a potentially beneficial addition to the treatment of septic shock
- More data is needed on short-term clinical outcomes and long-term adverse effects
V1a Receptor Agonists
Vasopressin Receptors

V1a (V1)
- Vascular smooth muscle
- liver, platelets, uterus, adrenal cortex
- Vasoconstriction, hepatic glycogenolysis, platelet aggregation

V2
- Collecting ducts of kidneys
- Endothelial cells
- Increased H2O reabsorption
  
  FVIII, vWF, and t-PA

V1b (V3)
- Anterior pituitary
- ACTH secretion

vWF = von Willebrand factor; t-PA = tissue plasminogen activator
Vasopressin in Septic Shock

- Initial spike followed by rapid decline of vasopressin levels
- Increases cortisol levels
- Coronary/pulmonary vasodilation via NO production
- Infusion effects: decreased norepinephrine doses, increased urine output/CrCl, and decreased cardiac output

NO = nitric oxide; CrCl = creatinine clearance
VASST

- Evaluated vasopressin (AVP) versus norepinephrine (NE) effect on 28 day mortality in septic shock
  - Multicenter, randomized, double-blind; N = 778
  - Stratified by baseline NE dose
  - No difference in primary outcome (35.4% vs. 39.3%)
    - Secondary outcomes: No difference in 90 day mortality, any organ dysfunction subgroup, or LOS
    - No difference in adverse effects

- Conclusions
  - AVP significantly decreased NE doses at day 4 (p < 0.001)
  - AVP MAY improve mortality in patients with less severe shock

LOS=length of stay
Terlipressin

- Synthetic analogue of lysine vasopressin
- 2x higher affinity for V1a receptor vs. V2 receptor
- Longer half-life (50 min vs. 6 min)
- Bolus and continuous infusion studied
- Meta-analyses show conflicting effects on mortality
- Therapeutic and adverse effects similar to vasopressin
- Not available in US

Terlipressin vs. NE for Septic Shock

- Multicenter, randomized, double-blind trial in 21 Chinese ICUs
  - Terlipressin 20-160 mcg/hr vs. NE 4-30 mcg/min
  - Target enrollment: 1100
  - Trial stopped after 50% enrollment due to futility
  - No difference in 28 day mortality (40% vs. 38%)
  - More adverse effects in terlipressin group (30% vs. 12%)
    - Primarily digital ischemia

Selepressin

- Selective V1a agonist
- Animal data demonstrates superiority over AVP and NE
  - Improved hemodynamic stability
  - Reduced lung edema and cumulative fluid balance
  - Preserved renal function
  - Attenuated coagulation disorders
  - Decreased systemic inflammation
  - May decrease vascular leakage
  - Improved survival

Selepressin in Early Septic Shock

- Phase II dose-finding study
  - Multicenter, randomized, double-blind, placebo-controlled; N=52
  - Patients with early septic shock randomized to 1 of 3 doses of selepressin or placebo
    - 3.75 ng/kg/min arm stopped due to safety concerns → N=50 patients in final analysis
  - Open-label NE to maintain MAP ≥ 60
- Primary endpoints: stabilization of MAP and cumulative NE doses

Results

<table>
<thead>
<tr>
<th></th>
<th>Selepressin 2.5 ng/kg/min (N=19)</th>
<th>Selepressin 1.25 ng/kg/min (N=10)</th>
<th>Placebo (N=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE-free at Hour 12</td>
<td>50%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>NE-free at Hour 24</td>
<td>70%</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>NE-free at Hour 48</td>
<td>70%</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>Cumulative NE dose at day 7</td>
<td>249 mg/kg</td>
<td>659 mg/kg</td>
<td>761 mg/kg</td>
</tr>
<tr>
<td>Alive and free of mechanical</td>
<td>54%</td>
<td>31%</td>
<td>23%</td>
</tr>
<tr>
<td>ventilation at day 7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Selepressin 2.5 ng/kg/min resulted in faster shock reversal and lower cumulative NE doses
- No difference in ICU or hospital LOS or 28 day mortality
- Adverse effects similar

SEPSIS-ACT

• Adaptive Phase IIb/III clinical trial of selepressin for septic shock
• Multicenter, randomized, blinded, placebo-controlled
• Evaluating up to 4 dosing strategies (1.7-5 ng/kg/min)
• Primary outcome: Pressor and ventilator-free days
• Target enrollment: 1800 patients
• Study terminated after 868 patients enrolled due to futility

Unanswered Questions

- Could alternate dosing strategies of terlipressin be beneficial?
- Results of SEPSIS-ACT?
Summary

- Vasopressin and its analogs (VA) are effective vasopressors and are catecholamine-sparing.
- Low-dose vasopressin appears to have fewer ADEs than other agents.
- VA may decrease the incidence of AKI in septic shock.
- Selective V1a agonism may provide additional benefit but more data is needed.
Conclusions

• Available evidence suggests strategies to decrease catecholamine exposure are necessary
• Many unanswered questions remain
  ▫ What is the ideal vasopressor “cocktail”?
  ▫ Does timing of vasopressor initiation matter?
  ▫ Should vasopressor studies use more clinically meaningful endpoints?
    • Days alive and free vs. 28 day mortality

Learning Assessment Questions

1. Clinical evidence supports the use of angiotensin II for the following:
   - A. Decreasing mortality in patients with septic shock
   - B. Increasing blood pressure in patients with vasodilatory shock
   - C. Increasing blood pressure in patients with cardiogenic shock
   - D. Improving organ dysfunction (i.e. decreasing SOFA score) in patients with septic shock
1. Clinical evidence supports the use of angiotensin II for the following:
   ▫ A. Decreasing mortality in patients with septic shock
   ▫ B. Increasing blood pressure in patients with vasodilatory shock
   ▫ C. Increasing blood pressure in patients with cardiogenic shock
   ▫ D. Improving organ dysfunction (i.e. decreasing SOFA score) in patients with septic shock

   Answer B is correct. The ATHOS-3 trial demonstrated a statistically significant increase in mean arterial pressure (MAP) within 3 hours in patients with vasodilatory shock.
2. Which of the following are potential advantages for the use of selepressin in patients with septic shock?

- A. Decrease in cumulative fluid balance
- B. Decreased time to resolution of shock
- C. Avoidance of procoagulant effects of V2 receptor agonism
- D. Decreased time on mechanical ventilation
- E. All of the above
2. Which of the following are potential advantages for the use of selepressin in patients with septic shock?

- A. Decrease in cumulative fluid balance
- B. Decreased time to resolution of shock
- C. Avoidance of pro-coagulant effects of V2 receptor agonism
- D. Decreased time on mechanical ventilation
- E. All of the above

Answer E is correct. Preliminary animal and human studies of selepressin have demonstrated all of the above effects. Larger studies are needed to confirm these effects.
Thank you!