Critical Care Collaborative
College of Pharmacy
UNIVERSITY OF GEORGIA

Real World Experiences with Angiotensin II in Refractory Shock

Zachary D. Halbig, PharmD Candidate; Susan E. Smith, PharmD, BCPS, BCCCP; Andrea S. Newsome, PharmD, BCPS, BCCCP; Shravan Kethireddy, MD

BACKGROUND

- Refractory shock is characterized by an inadequate response to conventional catecholamine vasopressors and is associated with increased mortality.
- Norepinephrine is considered the first line agent, most notably in distributive shock followed by vasopressin as the leading second line agent.
- A novel agent, Giapreza™ (Angiotensin II, ATII), was FDA approved in 2017 for refractory shock through ATHOS-3 trial.
- Safety and efficacy data from a pragmatic setting are lacking.
- This study describes two institution's real-world experiences with ATII, including prescribing information and patient outcomes.

OUTCOMES

Primary

- Characterize when, how, and in what patients ATII was prescribed.

Secondary

- Hemodynamic Response
- Incidence of Venous Thromboembolism (VTE)
- Inpatient mortality
- Drug Expenditure

STUDY DESIGN

- **Design**: IRB-approved, retrospective cohort study
- **Time Frame**: June 2018 to January 2019
- **Setting**: Northeast Georgia Health System (Gainesville and Braselton)
- **Inclusion Criteria:**
  - Adult Patients
  - Admitted to either facility
  - Received ATII
  - Vasopressors for longer than 3 hours
- **Identification of Patients**: Pharmacy dispensing records
- **Administration Confirmation:** Via chart review

RESULTS

Variable	n=34*
Age	68 (57 – 72)
Male Gender	14 (41)
Weight	103 (87 – 113)
Home ACEI/ARB	9 (26)
Distributive Shock	26 (76)
Indication for Vasopressors	
Septic shock	22 (65)
Cardiogenic shock	4 (12)
Combined septic and cardiogenic shock	3 (9)
Vasoplegia	3 (9)
Hypovolemic shock	1 (3)
Vasodilatory shock	1 (3)
Number of Vasopressors	3 (2 – 3)
Ordering location of angiotensin II	
Critical care unit	11 (32)
Cardiovascular intensive care unit	6 (18)
Medical intensive care unit	6 (18)
Surgery/trauma intensive care unit	6 (18)
Operating room	3 (9)
Intensive care unit	2 (6)
Ordering service of angiotensin II	
Critical Care	26 (76)
CT Surgery	3 (9)
Anesthesia	2 (6)
Trauma	2 (6)
Heart Failure	1 (1)
Initial angiotensin II Dose	10 (10 – 10)
Maximum angiotensin II Dose	55 (40 – 80)
Appropriate angiotensin II Dose Titration	21 (62)
Duration of angiotensin II (min)	1073 (223 – 3613)
Initial MAP (mmHg)	59 (53 – 70)
MAP after 3 h (mmHg)	74 (62 – 80)
Number of Vials of angiotensin II	2 (1 – 6)
Cost of angiotensin II ($)	3000 (1500 – 9000)
Time to reach MAP ≥ 65 mmHg (min)	16 (7 – 54)
Mortality	15 (44)
Venous thromboembolism prophylaxis	27 (79)
Venous thromboembolism	3 (9)

*Values presented as Median (Interquartile Range) or Number (Percent)
ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker;
MAP – mean arterial pressure

RESULTS CONTINUED

- Patients were receiving a median of three vasopressors at the time of ATII initiation
- Received ATII for a median of 18 hours
- Within 3 hours of ATII initiation, mean arterial pressure (MAP) increased by a median of 15 mmHg
- Median Time to reach MAP >65 was 16 minutes
- Twenty-Seven patients (79%) received VTE prophylaxis and three of these (9%) developed a VTE within 28 days
- Fifteen Patients (44%) did not survive to discharge
- Median Drug expenditure was $3000 per patient (cumulative expenditure $186,000)
- Trend towards higher mortality in patients with distributive shock compared to other shock states. (see chart below).

Covariate	Odds Ratio	95% Confidence Interval	p-value
Age	1.004	0.951 – 1.059	0.896
Female Gender	0.715	0.147 – 3.470	0.677
Concomitant ACEI/ARB	2.383	0.499 – 11.375	0.276
Distributive Shock	10.398	0.928 – 116.570	0.058
Number of Vasopressor Prior to ATII	1.128	0.392 – 3.246	0.823

Average Wholesale Price		
Drug	Amount	Price
Norepinephrine	1mg vial	$2.63
Vasopressin	20 unit vial	$215.75
Angiotensin II	2.5mg vial	$1800

CONCLUSIONS

- The study observed a positive hemodynamic response to ATII and a lower mortality rate in refractory states.
- Future research should compare the safety and efficacy of ATII to other second-line vasoactive agents (e.g., vasopressin).
- Limitations:
  - Small sample size
  - Retrospective design
  - Lack of control group
  - Absence of illness severity score
- Advantages:
  - Largest case series of ATII to date
  - Only one to include mixed shock states

REFERENCES

Giapreza [package insert]. San Diego, CA: La Jolla Pharmaceuticals; 2017.
Khanna, A., et al., Angiotensin II for the Treatment of Vasodilatory Shock. N Engl J Med, 2017. 377(5): p. 419-430.
Rhodes, A., et al., Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med, 2017. 43(3): p. 304-377.

Ideas:

Price comparison between ATII and NE
Lower VTE rate compared to ATHOS-3

Primary Outcome

- Characterize when, how, and in what patients ATII was prescribed.

Secondary Outcomes

- Hemodynamic Response
- Incidence of Venous Thromboembolism (VTE)
- Inpatient mortality
- Drug Expenditure