Published in final edited form as:

Pharmacotherapy. 2020 January ; 40(1): 33–39. doi:10.1002/phar.2346.

Vasopressin plasma concentrations are not associated with hemodynamic response to exogenous vasopressin for septic shock

Jason R. Yerke¹, Gretchen L. Sacha¹, Rachel G. Scheraga^{2,3}, Daniel A. Culver^{2,3}, Susamma Abraham³, Heather Torbic¹, Simon W. Lam¹, Mahmoud A. Ammar⁴, Mitchell A. Olman^{2,3}, Seth R. Bauer¹

¹Cleveland Clinic, Department of Pharmacy, Cleveland, OH, USA

²Cleveland Clinic, Respiratory Institute, Department of Pulmonary and Critical Care Medicine, Cleveland, OH, USA

³Cleveland Clinic, Lerner Research Institute, Department of Inflammation and Immunity, Cleveland, OH, USA

⁴Yale New Haven Health System, Department of Pharmacy, New Haven, CT, USA

Abstract

Introduction: Positive hemodynamic response to vasopressin after 6 hours of infusion was independently associated with lower mortality in a previous retrospective study of patients with septic shock. However, factors previously associated with higher plasma vasopressin concentration were not associated with response, and the relationship between plasma vasopressin concentration and hemodynamic response has not been evaluated.

Objectives: This cross-sectional study compared plasma vasopressin concentrations in hemodynamic responders and non-responders to vasopressin in patients with septic shock to evaluate plasma vasopressin concentration as a therapeutic target for hemodynamic response to vasopressin.

Methods: Adult patients with septic shock were included if they were treated with fixed-dose vasopressin as an adjunct to catecholamines for at least 3 hours. Patients were assigned to groups based on vasopressin response.

Results: Ten hemodynamic responders to vasopressin and eight non-responders were included. Blood samples for plasma vasopressin concentration were collected 3 to 6 hours after vasopressin initiation. Baseline characteristics were similar between groups. No difference was detected in plasma vasopressin concentrations between hemodynamic responders and non-responders (median 88.6 pg/ml [interquartile range (IQR) 84.4, 107.5 pg/ml] vs 89.9 pg/ml [IQR 67.5, 157.4 pg/ml],

Corresponding Author: Jason R. Yerke, 9500 Euclid Ave., Hb-105, Cleveland, OH, USA, 44022; telephone: 216-379-4610; yerkej@ccf.org.

Conflict of Interest Statement: Seth R. Bauer reports receiving consultancy fees from Wolters Kluwer. The remaining authors report no actual or potential conflicts of interest in relation to this study.

This work was performed at Cleveland Clinic.

p=0.79, respectively). We also did not detect a difference between groups after correcting for vasopressin dose; median vasopressin plasma concentration per 0.01 units/min of vasopressin infusion for responders was 25.9 pg/ml (IQR 21.8, 31.8 pg/ml) versus 29.5 pg/ml (IQR 23.0, 57.5 pg/ml, p=0.48) for non-responders. No difference in clinical outcomes was detected between groups. The findings were robust to multiple sensitivity analyses.

Conclusions: This study does not support the use of plasma vasopressin concentrations as a therapeutic target to predict hemodynamic response to exogenous vasopressin in septic shock.

Keywords

septic shock; endocrinology; pharmacodynamics; pharmacokinetics

Introduction

As part of the stress response to hypotension, vasopressin is released from the posterior pituitary and leads to vasoconstriction through agonism of the vascular vasopressin V1 receptor.¹ In patients with septic shock, endogenous vasopressin concentrations are initially elevated but quickly fall to concentrations at or below those seen at homeostasis because of the depletion of endogenous stores.¹⁻³ Furthermore, endogenous vasopressin concentrations have been shown to be lower in patients with septic shock compared to other shock etiologies.^{1, 3} As such, exogenous arginine vasopressin (AVP) has been used as an adjunct to exogenous catecholamines in order to increase mean arterial pressure (MAP), and to decrease catecholamine requirements in patients with vasodilatory shock.^{4, 5} However, the pharmacodynamics of exogenous AVP have not been clearly established.

Hemodynamic response to AVP after 6 hours of infusion has been independently associated with lower mortality in patients with septic shock, and may represent a short-term therapeutic target.⁶ Some have theorized that an optimal plasma vasopressin concentration exists for patients with septic shock, and targeting this concentration with exogenous vasopressin could improve clinical outcomes.⁷ However, a definitive relationship between plasma vasopressin concentration achieved with exogenous AVP and hemodynamic response has not been demonstrated. This study sought to determine the relationship between plasma vasopressin concentrations and hemodynamic response in patients receiving fixed-dose AVP for septic shock.

Materials and Methods

We conducted a prospective cross-sectional study evaluating single plasma vasopressin concentrations in patients with septic shock ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03014063) number NCT03014063; the rationale for study registration after enrollment of the first patient can be found in the supplementary appendix). The study was conducted in the medical, surgical, and neurologic intensive care units (ICU) at a large academic medical center in Cleveland, Ohio from November 2016 to June 2017. Adult patients 18 years of age and older were included if they met criteria for septic shock.⁸ Patients were also required to receive fixed-dose, exogenous AVP for a minimum of 3 hours as adjunctive therapy to catecholamine vasopressors as ordered by the primary care team, and to have a central venous catheter or arterial catheter in

place. Patients were excluded if they received AVP for an indication other than septic shock, if AVP was titrated prior to when the study team was able to collect a blood sample, if AVP was used as the sole vasoactive therapy, if AVP was initiated prior to arrival of the patient at the study site, or if the patient or patient's representative opted to remove the patient from the study (Figure 1). Blood samples were collected from eligible patients 3 to 6 hours after AVP initiation. The bedside nurse was instructed to procure the sample from a port proximal to the infusion of vasopressin. Although this does not entirely eliminate the possibility of a sample being drawn from the lumen in which vasopressin is being infused, it does minimize the risk. Single blood samples were collected from eligible patients via a previously-placed catheter into chilled EDTA test tubes (Becton Dickinson, Franklin Lakes, NJ) and placed on ice. Blood samples were immediately transported to a research laboratory and centrifuged at 4°C for 15 minutes at 1600g. Plasma was stored at -70°C until the time of analysis. Plasma was analyzed for vasopressin concentration with the Enzo Life Sciences Arg⁸-Vasopressin enzyme-linked immunosorbent assay kit (Enzo Life Sciences, Farmingdale, NY) following the recommended extraction procedure. Per the manufacturer's instructions, all samples were analyzed with and without the addition of a known quantity of vasopressin to determine the percentage recovery upon extraction.^{9, 10} Reported vasopressin concentrations were corrected for the percentage recovery of the known quantity of vasopressin (e.g., if the concentration reported by the assay was 50 pg/ml and the recovery was 50%, the plasma concentration was reported as 100 pg/ml).^{9, 10} This correction of individual samples was performed because the percentage yield varied widely (from 45.1% to 95.0%), but mostly within the assay manufacturer's expected range (median recovery yield of the known quantity of vasopressin was 59.6% [interquartile range (IQR) 49.7%, 72.2%]).⁹

The primary objective was to compare plasma vasopressin concentrations between hemodynamic responders and non-responders to AVP. Hemodynamic response was defined as a MAP of 65 mm Hg or higher and a decrease in catecholamine dose (expressed in norepinephrine equivalents) from the time of AVP initiation to the time of the blood draw for the plasma vasopressin concentration.⁶ Secondary objectives included evaluating the correlation of plasma vasopressin concentration with catecholamine dose change between the time of AVP initiation and plasma sample collection, and comparing responders to non-responders in regards to ICU and in-hospital mortality, vasopressor-free days at day 14, and ICU-free days at day 14 (day 1 for vasopressor- and ICU-free days was considered the day of AVP initiation).

Assuming a mean vasopressin concentration of 100 pg/ml in responders and 70 pg/ml in non-responders with a standard deviation of 20 pg/ml in each group and an allocation ratio of 1, 18 patients (9 per group) were needed to achieve 80% power with $\alpha = 0.05$.^{4, 11} χ^2 or Fisher exact test were used to evaluate nominal variables, as appropriate. Student *t* test was used to evaluate normally distributed continuous variables, and Wilcoxon rank-sum test was used to evaluate non-normally distributed continuous variables. Correlation was assessed with Pearson correlation. All statistical analyses were performed with Stata 14 (StataCorp LLC, College Station, TX) with *p* values less than 0.05 considered statistically significant. This study was approved by the Cleveland Clinic Institutional Review Board with a waiver of informed consent, and was conducted according to the Declaration of Helsinki.

Results

A total of 18 patients were included; 10 hemodynamic responders and 8 non-responders (Figure 1). Overall, patients were severely ill with median (IQR) Acute Physiology and Chronic Health Evaluation III score of 115.5 (85, 128), sequential organ failure assessment score of 12.5 (10, 16), and norepinephrine-equivalent dose of 36.5 µg/min (20, 50 µg/min) at AVP initiation. No differences were detected between responders and non-responders in baseline characteristics (Table 1). The most common admission ICU type for included patients was medical followed closely by surgical. Nearly all patients in each group were receiving concomitant corticosteroids at the time of AVP initiation.

No difference was detected in plasma vasopressin concentrations between groups; responders had a median concentration of 88.6 pg/ml (IQR 84.4, 107.5 pg/ml) versus a median concentration of 89.9 pg/ml (IQR 67.5, 157.4 pg/ml, $p=0.79$) in non-responders (Figure 2). Furthermore, no difference between groups was detected after correction for the AVP infusion dose (median vasopressin plasma concentration per 0.01 units/min of AVP infusion for responders 25.9 pg/ml [IQR 21.8, 31.8 pg/ml] vs non-responders 29.5 pg/ml [IQR 23.0, 57.5 pg/ml], $p=0.48$). Higher vasopressin plasma concentrations did not correlate with a decrease in catecholamine doses (Figure 3). No difference was detected when comparing responders to non-responders in regards to ICU mortality (5/10 [50%] vs 4/8 [50%], $p=1.0$), in-hospital mortality (5/10 [50%] vs 5/8 [62.5%], $p=0.66$), vasopressor-free days at day 14 (11 days [IQR 0, 11 days] vs 4.5 days [IQR 0, 10.5 days], $p=0.45$), or ICU-free days at day 14 (0 days [IQR 0, 5 days] vs 2 days [IQR 0, 6.5 days], $p=0.51$), respectively.

Several sensitivity analyses were conducted to evaluate the robustness of the findings. After removing the patient with the highest plasma vasopressin concentration (the most striking outlier), no difference in plasma vasopressin concentrations was observed between groups (responders median 88.6 pg/ml [IQR 84.4, 107.5 pg/ml] vs non-responders median 79.9 pg/ml [IQR 58.3, 119.3 pg/ml], $p=0.44$), and no correlation between plasma vasopressin concentration and change in catecholamine dose was observed ($r = -0.11$, $p=0.66$). Similarly, when removing the patients with the three highest plasma vasopressin concentrations (those with plasma vasopressin concentration above the 75th percentile of what was reported 24 hours after randomization in the Vasopressin and Septic Shock Trial [VASST])⁴, no difference in plasma vasopressin concentrations was observed (responders median 87.3 pg/ml [IQR 84.4, 100.0 pg/ml] vs non-responders median 78.3 pg/ml [IQR 58.3, 99.8 pg/ml], $p=0.24$), and no correlation between plasma vasopressin concentration and change in catecholamine dose was observed ($r = -0.22$, $p=0.44$).

Discussion

This cross-sectional study of patients with septic shock receiving exogenous AVP did not detect a difference in plasma vasopressin concentrations between hemodynamic responders and non-responders to AVP. Even after correcting for AVP infusion dose no difference in plasma vasopressin concentrations was detected between groups. Our data do not support the hypothesis of an ideal vasopressin plasma concentration leading to improved rates of

hemodynamic response, a short-term outcome that has previously been associated with lower rates of mortality in patients with septic shock treated with adjunctive AVP.⁶ In fact, our findings suggest hemodynamic response to AVP in patients with septic shock is likely determined by factors other than plasma vasopressin concentration. Although arterial lactate at the time of AVP initiation did not meet our pre-specified p-value for a statistically significant difference between responders and non-responders, there was a striking numerical difference between hemodynamic responders (median 1.6 mmol/L, IQR 1.3 to 5.7 mmol/L) and non-responders (median 4.1 mmol/L, IQR 2.5 to 4.8 mmol/L, $p=0.28$). Notably, previous literature has observed a lower lactate at AVP initiation or study enrollment in subsets of patients deriving clinical benefit from AVP in septic shock.^{6, 12} Lower lactate levels may indicate hyperdynamic circulation with intact coupling of the macrocirculation to the microcirculation, conditions in which patients with septic shock may be most likely to benefit from AVP.¹³

The vasopressin concentrations in the current study were similar to those in VASST, which found that AVP infused at a dose of 0.01 to 0.03 units/min led to plasma vasopressin concentrations of 79.5 pg/ml (IQR 63.3, 102.3 pg/ml) at 6 hours and 105.8 pg/ml (IQR 72.5, 138.0 pg/ml) at 24 hours after AVP initiation.^{4, 11} The vasopressin concentrations achieved in VASST after AVP initiation and observed in the current study far exceed the endogenous concentrations observed in other shock states (22.7 ± 2.2 pg/ml in patients with cardiogenic shock), those observed in VASST prior to initiation of exogenous AVP (3.5 pg/ml [IQR 1.8, 5.3 pg/ml]), and those observed in a cohort of patients with early sepsis (range of 4.1–21.0 pg/ml collected 3.6 ± 2.3 hours after sepsis onset) and represent the use of AVP beyond the requirements for endocrine replacement therapy.^{2, 4, 11} Although our study included a limited sample, no association was identified between vasopressin plasma concentration and hemodynamic response. Because of this, use of vasopressin plasma concentration as a therapeutic target cannot be supported based on our data.

The current study findings contrast those from a study demonstrating lower norepinephrine requirements over time and higher vasopressin plasma concentrations in patients treated with 0.067 units/min versus 0.033 units/min of AVP for advanced vasodilatory shock.¹⁴ There are notable differences, though, in patient population and vasoactive therapy approaches compared with the current study. In the referenced study, only about half of the patients had septic shock and patients were only enrolled if they were receiving a norepinephrine dose above $0.6 \mu\text{g/kg/min}$.¹⁴ This norepinephrine dose is higher than the norepinephrine dose at AVP initiation for 13 of the 18 patients included in the current study of patients exclusively with septic shock. A case series observed larger increases in MAP when AVP was used with a catecholamine than when it was used alone in septic shock, suggesting that AVP potentiates the activity of catecholamines.¹⁵ It is likely that the vasopressin plasma concentration required to achieve this potentiation differs based on severity of shock. Additionally, although only one patient in the current study was treated with concomitant epinephrine, most patients in the study evaluating 0.067 units/min versus 0.033 units/min of AVP for advanced vasodilatory shock were treated with milrinone and/or epinephrine, agents known to have hemodynamic effects influencing norepinephrine requirements.¹⁴ As such, the influence of achieved vasopressin plasma concentrations on response to AVP in patients

with advanced septic shock and/or those treated with concomitant inotropic agents is unclear.

This study is limited by the lack of vasopressin concentration sampling prior to exogenous AVP initiation. However, at baseline (about 12 hours after shock onset) in VASST, patients had median vasopressin concentrations of 3.5 pg/ml (IQR 1.8, 5.3 pg/ml).^{4, 11} These low concentrations and narrow IQR coupled with similar timing of AVP initiation after shock onset as in the current study give confidence that the observed vasopressin concentrations in the current study can be largely attributed to the exogenous AVP infusion. Additionally, although the target sample size was achieved, attrition in enrollment was high and the power analysis was based on a vasopressin concentration difference of 30 pg/ml between groups. Therefore, we are only able to exclude a relatively large difference in vasopressin concentrations between hemodynamic responders and non-responders to AVP. Also, a change in the directionality of correlation between plasma vasopressin concentration and change in catecholamine dose (from +0.71 to -0.22) was observed when excluding the most striking outliers, although the negative correlation was not statistically significant. Because of the small sample size of our study, the ability to detect a statistically significant but small in magnitude correlation between vasopressin plasma concentration and change in catecholamine dose is limited. Furthermore, we are unable to establish the temporality between vasopressin plasma concentrations and hemodynamic response to exogenous vasopressin. Finally, our results may only be generalizable to patients with high catecholamine requirements given the high catecholamine doses at baseline in this study. Results may differ in patients with less severe shock.

Conclusions

Although response to AVP in patients with septic shock has been associated with improved outcomes,⁶ the plasma vasopressin concentration achieved with AVP is not associated with hemodynamic response. This study does not support the use of plasma vasopressin concentration as a therapeutic target for predicting hemodynamic response to AVP in septic shock.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

Financial support for this project was provided by the Cleveland Clinic Department of Pharmacy to Seth R. Bauer, National Institute of Health grants HL-133721 and HL-119792 to Mitchell A. Olman, and National Institute of Health grant HL-133380 to Rachel G. Scheraga.

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Figure 1:
Population assessed for eligibility
AVP, arginine vasopressin

Figure 2:

Vasopressin plasma concentration by hemodynamic response

Vasopressin 1 pg/ml = 0.923 picomoles per liter. pg/ml, picograms per milliliter

Figure 3:

Change in catecholamine dose by corrected plasma vasopressin concentration

Correlation between vasopressin plasma concentration and change in catecholamine dose $r = +0.71$ ($p < 0.01$), indicating an increase in catecholamine dose with higher vasopressin plasma concentrations. Vasopressin 1 pg/ml = 0.923 picomoles per liter. mcg/min, micrograms per minute; pg/ml, picograms per milliliter; AVP, arginine vasopressin.

Table 1.**Baseline Characteristics of the Study Population**

	Responders (n=10)	Nonresponders (n=8)	p
Age, yrs	58.2 ± 12.5	60.2 ± 14.4	0.77
Male sex	6 (60)	6 (75)	0.64
Weight, kg	92.4 ± 28.4	84.9 ± 22.0	0.55
BMI, kg/m ²	31.2 ± 8.8	29.1 ± 9.4	0.63
ICU type			
Medical	5 (50)	4 (50)	1.0
Surgical	4 (40)	3 (37.5)	
Neurologic	1 (10)	1 (12.5)	
APACHE III	106.6 ± 38.0	114.9 ± 45.4	0.68
SOFA	12.8 ± 2.7	12.8 ± 4.1	0.98
Lactate at AVP initiation, mmol/L	1.6 (1.3–5.7)	4.1 (2.5–48)	0.28
Broad-spectrum antibiotics at AVP initiation	10 (100)	7 (87.5)	0.44
Bolus crystalloid volume administered from AVP initiation through the time of blood sample collection, ml	0 (0–1000)	0 (0–500)	0.45
Bolus albumin volume administered from AVP initiation through the time of blood sample collection, ml	0 (0–0)	0 (0–500)	0.40
Concomitant corticosteroid therapy at AVP initiation	9 (90)	8 (100)	1.0
MAP at AVP initiation, mm Hg	65.3 ± 7.0	62.0 ± 4.7	0.27
AVP dose			
0.02 units/min	1 (10)	2 (25)	0.57
0.03 units/min	3 (30)	3 (37.5)	
0.04 units/min	6 (60)	3 (37.5)	
Norepinephrine equivalents at AVP initiation, µg/min	36.5 (17–56)	35 (20–50)	0.77
Time from catecholamine initiation to AVP initiation, hrs	10.7 (6.3–37.4)	6.4 (2.2–28.9)	0.29
MAP at time of blood sample, mm Hg	71.9 ± 4.1	66.6 ± 10.3	0.21
Arterial pH at time of blood sample collection	7.38 (7.30–7.40)	7.36 (7.22–7.37)	0.20
KDIGO stage 2 or 3 acute kidney injury at AVP initiation ^a	6/8 (75)	5/8 (62.5)	1.0
Lactate at time of blood sample, mmol/L	2.1 (1.2–3.7)	4.8 (3.5–6.1)	0.10
Norepinephrine equivalents at time of blood sample, µg/min	16 (5–34)	39 (9–60)	0.20
Time from catecholamine initiation to blood sample, hrs	16.1 (12.0–42.7)	9.5 (6.4–33.5)	0.18
Time from AVP infusion initiation to blood sample, hrs	4.7 ± 0.9	4.2 ± 1.1	0.27

Data presented as n (%), mean ± standard deviation, or median (interquartile range), as appropriate.

APACHE III – Acute Physiology and Chronic Health Evaluation III score; AVP – arginine vasopressin; BMI – body mass index; ICU – intensive care unit; KDIGO = Kidney Disease Improving Global Outcomes; MAP = mean arterial pressure; SOFA = Sequential Organ Failure Assessment.

^aTwo patients in the responders group had end-stage renal disease at baseline and were not included in this analysis.