CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review of the Individual Studies

NDA Number:	**204485**
Submission Type; Code:	**S, 505 (b)(2)**
Applicant Name:	**JHP Pharmaceuticals**
Submission Date:	**9-25-12**
Brand Name:	**Pitressin®**
Generic Name	(b) (4) (b) (4) **vasopressin**
Dosage Form:	**Intravenous injection**
Dosage Strengths:	**20 Pressor Units/mL in water**
Proposed Indication:	**Vasodilatory shock (including post-cardiotomy shock and septic shock)**
OCP Division:	**DCRP, HFD 110**
Primary Reviewer:	**Peter Hinderling, MD**
Team Leader:	**Rajnikanth Madabushi, PhD**

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1. PK in Healthy Adults

1.1

Publication	**Study Period:** Not indicated	**EDR Link**
Title	Urinary and Metabolic Clearances of Arginine Vasopressin in Normal Subjects. Moses AM, Steciak E. Am J Physiol. 1986; 251:R365-370	
Study Design: Eleven healthy subjects (6 males and 5 females) in the age between 18 and 37		

Reference ID: 3313815

years are investigated. At 0800 each subjects is given on oral water load of 20 mL/kg. Constant infusions of 0, 10, 35, 100, 200 and 350 µU● kg/min over 60 min are given to the subjects. During the infusions the subjects void every 30 min and the amount avoided is replaced by tap water. Several subjects were unable to void in 30 min intervals and these studies were not completed.		
Rationale: The relationship between plasma and urine AVP concentrations and on renal and metabolic clearances of AVP in humans under steady-state conditions		
Objectives: To determine metabolic and urinary clearances under steady-state conditions		
Screening: Not indicated		**Washout:** None
Periods	6	
Treatment: Intravenous infusions of AVP		
Sequence	Fixed	
Dose Selection: 0**,** 10, 35, 100, 200 and 350 µU● kg/min		
Investigational Drugs and Formulations: Pitressin, Parke-Davis, Morris Plains, NJ for injection		
Administration: Repeat ascending dose intravenous infusion of arginine-vasopressin (AVP)		
Fed/Fasted: NI		
Interfering Substances: Ingestion of alcohol and smoking was not permitted for 12 h before study start		
PK Sampling Times: Blood for the determination of the plasma concentrations of AVP is collected at 30 and 60 min during each infusion. The steady-state concentration was measured 60 min into the infusions**.** Aliquots of urine from the second 30 min interval of each period are collected for measuring the concentrations of AVP.		
PD Sampling Times: 60 min into infusions of AVP		

Reference ID: 3313815

Analytical Method

PK

The plasma and urine samples to be assayed for AVP are extracted on Sep-PakC18 columns (waters Associates, Milford, MA) using methanol for the elution. The AVP concentrations in the test samples of AVP are measured by a RIA using the method and reagents (including ^{125}I-AVP, first and second antibodies in AVP radio-immuno kits provided by Immuno Nuclear (Stillwater, MN). The first antibody is stated to cross-react with oxytocin at 0.01% and with vasotocin at 0.14%. The same batch of AVP administered to the subjects is also used to set up the standard curves. The maximum sensitivity of the RIA standard curve is 1.49 µU/mL. Inter- and intra-assay coefficients of variation are 8.6 and 12.3%, respectively. The standard curves using Pitressin® were identical with curves constructed from AVP obtained from Sigma Chemical (St. Louis, MO), Calbiochemical (San Diego, CA), and the World Health Organization International AVP standard. The standard provided by Immuno Nuclear is 1.9 times as active as the above standards.

Analyte		AVP
Method		RIA
Matrix		Plasma and Urine
Range, ng/mL		Not indicated
Quality Control	% CV	Not indicated
	%RE	Not indicated

NI=not indicated

Blood is collected into evacuated glass tubes and chilled immediately, centrifuged immediately and brought to pH 3.5 with acetic acid. The plasma and urine samples are stored at -20 ˚C for < 2 months until assaying. The AVP remaining in the dead space of the infusion tubing exhibited the calculated potency indicating that no AVP adhered to the plastic bag or tubing.

PD

Osmolality in urine was determined using a freezing point depression osmometer.

Target PK Parameters: "Metabolic" (=total) clearance, CL, and "urine" (=renal) clearance, CL_R

PK Data Analysis: Total clearance was determined by dividing the infusion rate (ko) by the plasma concentration of AVP at the end of each 60 min infusion period. The renal clearance was obtained from dividing the excretion rate by the steady-state plasma concentration. Baseline concentrations representing endogenous AVP were not measured. The tacit assumption was made that secretion of endogenous AVP would cease rapidly after initiation of the infusions with exogenous AVP so that AVP measured at 60 min would reflect only exogenous AVP. Also, the subjects were hydrated so that the concentrations of endogenous AVP would be minimal.

Target PD Parameters: Osmolality in urine, pulse rate, systolic and diastolic blood pressure (BP)

Statistical Method: Not indicated

Sample Size/Power: The selected sample size was not based on power considerations.

Results

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Study Population:

Randomized Treated Completed Discontinued: withdrawal from study at request of subject Pharmacokinetic population Safety population	11 11 11 0 11 11
Age [Range], years	18-37
Weight [Range], kg	65-70
Male/Female	6/5
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated

PK

The below table lists the plasma concentrations at 30 and 60 min of infusion and the amounts of AVP excreted in urine over the 60 min:

Mean(SEM) Plasma Concentrations and Amounts of AVP Excreted into Urine at Steady-State

Infusion Rate	Plasma concentration		Urine Excretion Rate
	30 min	60 min	
μU/kg/min	μU/mL	μU/mL	μU/min
0	NI	NI	5.42 (1.50)
10	2.64 (0.44)	2.49 (0.42)	45.4 (7.4)
35	3.98 (0.53)	4.56 (0.71)	155 (29)
100	9.40 (0.97)	9.71 (0.95)	439 (37)
200	14.6 (1.82)	15.8 (2.10)	790 (75)
350	26.8 (2.36)	21.6 (2.06)	1668 (205)

NI=Not indicated

The plasma concentrations appear to have attained at steady-state after 30 min of continuous infusion at all infusion rates, suggesting that the apparent disposition t1/2 does not exceed 7 min.

The below Fig. 2A shows a linear plot of the plasma concentration versus the infusion rate for AVP:

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There plasma concentrations of AVP increase apparently linearly with increasing infusion rates, only at the highest infusion rate. Only at the highest rate the plasma concentrations increase less than proportionally.

The below figures show linear plots of CL_R or CL vs. the infusion rate:

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The below table lists mean CL and CL_R and their ratio:

Mean (SEM) Total and Renal Clearances in Healthy, Young Subjects Receiving Infusion Rates of 0, 10, 35, 100, 200 and 350 μU/kg/min

Infusion Rate	CL	CL_R		CL_R/CL
μU/kg/min	mL/min/kg	mL/min	mL/kg/min	
0	NI*	NI*	NI*	
10	6.8 (2.3)	25.2 (6.8)	0.39 (0.11)	0.065
35	7.8 (0.7)	28.5 (2.9)	0.41 (0.05)	0.063
100	12.3 (2.2)	47.7 (3.5)	0.70 (0.08)	0.063
200	15.4 (2.2)	56.9 (7.4)	0.82 (0.11)	0.057
350	17.9 (2.0)	78.2 (6.8)	1.13 (0.10)	0.069

*NI=not indicated

The results indicate that both, CL and CL_R, increase proportionally with increasing infusion rate suggesting that a common mechanism impacts both, CL_R and CL. The CL ranges dose dependently between 440 and 1235 mL/min and CL_R between 25 and 78 mL/min when the infusion rate is increased from 10 to 350 μU/kg/min. The mechanism responsible for the increased CL could be either self-induction of the elimination rate constant or alternatively indicate dose dependent increase in volume of distribution. The ratio of CL_R to CL indicates that 6% of the dose is excreted unchanged by the kidney and the remainder is eliminated by metabolism or excretion into bile. The dose independence of this ratio indicates that CL_R and metabolic clearance are similarly increasing with dose.

PD and PK-PD

The below figures show the dose-response-relationship and the concentration-response relationship for AVP and urine osmolality:

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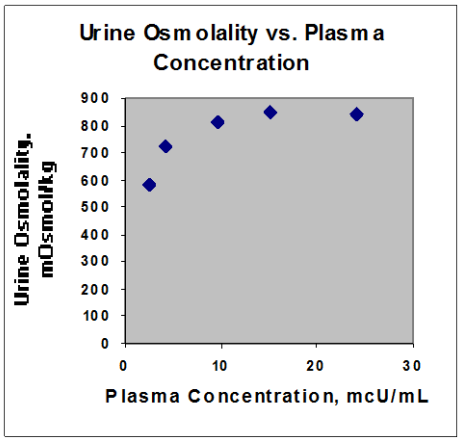

The exposure-response relationship shows saturability of the response with increasingly smaller increments in osmolality with higher infusion rates or plasma concentrations of AVP. At infusion rates > 200 µU/kg/min and concentrations exceeding 17 µU/mL, a maximum response on osmolality in urine is obtained.

The below table lists pulse rate and systolic and diastolic BP:

Mean(SEM) Pulse Rate and Systolic and Diastolic Blood Pressure

Infusion Rate	Pulse Rate	Systol. BP	Diastol. BP
µU/kg/min	beats/min	mmHg	mmHg
0	61(4)	116 (2)	71 (4)
10	66(4)	115 (2)	73 (3)
35	62 (2)	113 (3)	67 (3)
100	61 (4)	114 (3)	68 (3)
200	61 (4)	112 (4)	66 (4)
350	65 (5)	118 (3)	70 (3)

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The infusions of AVP did not impact BP or pulse rate, creatinine clearance or solute excretion.
Safety
▪ Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
Conclusion
• Steady-state is attained after a 30 min infusion suggesting t1/2 of AVP ≤ 10 min at all infusion rates • Disposition of AVP appears to be mainly by metabolism while renal excretion of unchanged AVP is minor • Both CL and CL_R appear to increase with increasing infusion rate, however the ratio of CL_R to CL remains constant suggesting the observed increase in CL and CL_R is due to an increase in V_D at higher infusion rates • AVP does not impact pulse rate or BP, creatinine clearance or solute excretion in the healthy subjects at the tested dose range
Comments
• None

1.2

Report #	Study Period	EDR Link
Title	Effect of Sodium Intake, Furosemide, and Infusion of Atrial Natriuretic Peptide on the Urinary and Metabolic Clearances of Arginine Vasopressin in Normal Subjects. Moses AM, Jones C, Yucha CB. J Clin Endocrinol Metab 1990;70:222-229	
Study Design: 3 studies were performed: the first study used a randomized crossover design and enrolled nine healthy young subjects of either sex. Each subject was studied once after intake of a diet containing 250 mEq/day for 4 days and once after intake of 10 meq sodium/day for 4 days. After an overnight fast the subjects received an oral water load of 20 mL/kg over 15-20 min. Urine was passed spontaneously every 15 min and the volume voided was replaced orally with tap water. After 3 consecutive periods of constant diuresis serial intravenous infusion of 10, 35 and 100 µU/kg/min AVP lasting 60 min were administered. During the infusions subjects voided every 30 min, and the voided volume was replaced by tap water. The second study used also a randomized crossover design and enrolled healthy, young male and female subjects. Five of the subjects participating in the second study were enrolled in the first study. The subjects were twice placed on a 250 meq/day diet and after an oral water load of 20 mL/min received serial infusions of 10 and 35 µU/kg/min AVP lasting 60 min. The study proceeded as described with the first study except that each subject was once infused with 40 mg furosemide intravenously over a 5 min period at the beginning of the first rate of infusion of AVP. The third study enrolled 10 young, healthy subjects who did not participated in the first or second study. They were placed on a 50 meq sodium diet for 4 days. After an oral water load of 20 mL/kg they were infused with 35 µU/kg/min AVP for 150 min. During the last hour they were also infused with 20 µg of 28-mino acid human αANP. The same experiment was subsequently conducted in 9 healthy subjects but with the infusion of 40 µg αANP.		
Rationale: To clarify the roles of sodium excretion, solute excretion, urinary volume,		

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plasma volume, atrial natriuretic peptide (ANP) and plasma renin activity (PRA) on total and renal clearance of AVP μg ANP.

Objectives: Primary: The goal of the first study was to determine the effect of sodium on the exposure and response to AVP. The goal of the second study was to determine the effect of furosemide on the response to infused AVP. The goal of the third study was to determine the effect of infused ANP on the response to AVP.

Screening: Not indicated	**Washout:** Not indicated
Periods	Experiments 1 and 2 have 2 periods

Treatments: Experiment 1**:** Infusion rates of AVP 10, 35 and 100 μU/kg/min AVP, with subjects placed on a 10 or 250 meq/day sodium diet, Experiment 2: Infusion rates of 10 or 35 μU/kg/min AVP, in presence or absence of 40 mg furosemide, subjects placed on a 250 meq/day sodium diet, Experiment 3: Infusion rate of 35 μU/kg/min AVP in presence and absence of 20 or 40 ANP

Sequence	Sequential conduct of experiments 1, 2 and 3

Dose Selection: The infusion rates used were those employed in previous experiments an shown to exert pharmacological activity and to be safe.

Investigational Drugs and Formulations: Synthetic AVP (Pitressin®, Parke-Davis), Furosemide, ANP

Administration: AVP, furosemide and ANP were administered by intravenous infusion.

Fed/Fasted: Not indicated

Interfering Substances: No medication including oral contraceptives other than study medications were allowed. Females were studied during the first half of the menstrual cycle. The subjects were instructed not to take alcohol for 48 h prior to study start and to refrain from alcohol intake for at least 12 h before study start.

PK Sampling Times: In the experiments blood samples for the determination of the plasma concentrations of AVP, PRA, ANP, and creatinine were collected 30 and 60 min into the infusions. Total urine volumes were collected during the second 30 min collection period of each infusion rate.

PD Sampling Times: Plasma osmolality was determined 30 and 60 minutes into the infusions and urine osmolality was determined in the second 30 min collection interval.

Analytical Method

Analyte		AVP
Method		RIA
Matrix		Plasma, Urine
Range, ng/mL		Not indicated
Quality Control	%CV	Not indicated
	%RE	Nor indicated

Blood for assaying was collected into evacuated glass tubes, chilled immediately, and centrifuged, and the plasma stored at -20°C for no longer than 2 months. After thawing the pH was adjusted by addition of 0.1 mL 1 n HCL/mL. Urine was acidified to pH 3.5. Plasma and urine were then extracted on Sep Pak C18 columns and eluted with methanol. The extraction recovery ranged from 83 to 92%. The RIA used a Ferring K3 antibody. The

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standard curves used the same batch of AVP that was used for the infusions. The maximum sensitivity of the standard curve was 0.4 μU/mL. Intra-and inter-assay coefficients of variation were 4.6 and 6.8%, respectively. The AVP obtained from infusion tubing when assayed exhibited the expected potency suggesting no adherence of AVP to the plastic bag or tubing. The plasma concentrations of ANP and PRA were determined by RIA. Osmolality was measured by a freezing point depression based osmometer.
Target PK Parameters: CL, CL_R, Css. The Css was measured 60 min into the infusions.
PK Data Analysis: CL= ko/Css, where Css is the plasma concentration of AVP at 60 min into the infusion. Attainment of steady-state after 60 min infusions of AVP was demonstrated by (1). Total clearance was determined by dividing the infusion rate (ko) by the plasma concentration of AVP at the end of each 60 min infusion period. The renal clearance was obtained from dividing the excretion rate by the steady-state plasma concentration. Baseline concentrations representing endogenous AVP were not measured. The assumption was made that secretion of endogenous AVP would cease rapidly after initiation of the infusions with exogenous AVP so that AVP measured at 60 min would reflect only exogenous AVP. Also, the subjects were hydrated so that concentrations of endogenous AVP would be minimal.
Target PD Parameters: Osmolal clearance
Statistical Method/ Sample Size/Power: The target parameters from paired studies were analyzed by analysis of variance for repeated measures to determine the effect of treatment at all infusion rates of AVP. The effects of AVP in the presence and absence of ANP were analyzed by paired one-tailed t-tests on the hypothesis that ANP would increase AVP clearance. The samples size was not based on statistical considerations.
Results

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Study Population:

Study 1

Randomized Treated Completed Discontinued Pharmacokinetic/dynamic population Safety population	9 9 9 0 9 9
Age [Range], years	23-37
Weight [Range], kg	Not indicated
Male/Female	7/2
Race (Caucasian/Black/Hispanic/Asian/Other)	Not indicated

Study 2

Randomized Treated Completed Discontinued Pharmacokinetic/dynamic population Safety population	9 9 9 0 9 9
Age [Range], years	23-37
Weight [Range], kg	Not indicated
Male/Female	8/1
Race (Caucasian/Black/Hispanic/Asian/Other)	Not indicated

Study 3

Parallel Group Study Group 1 Treated Completed Discontinued Pharmacokinetic/dynamic population Safety population	 10 10 10 0 10 10
Age [Range], years	22-40
Weight [Range], kg	Not indicated
Male/Female	8/1
Race (Caucasian/Black/Hispanic/Asian/Other)	Not indicated
Group 2 Treated Completed Discontinued Pharmacokinetic population Safety population	 9 9 0 9 9
Age [Range], years	23-42
Weight [Range], kg	Not indicated
Male/Female	7/2
Race (Caucasian/Black/Hispanic/Asian/Other)	Not indicated

PK

Study 1

The below table summarizes the mean CL, CL_R, steady-state concentrations and the

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fraction excreted unchanged of AVP in subjects placed on a µ250 meq or 10 meq/day containing sodium diet:

Mean (SEM) Steady-State Plasma Concentrations, Total, Renal Clearances and Fraction of AVP Excreted Unchanged in Urine in Subjects on a 250 or 10 meq/day Sodium Diet

Infusion Rate µU/kg/min	Sodium meq/day	Css µU/mL	CL mL/kg/min	CL_R[b] mL/kg/min	Ae/D[a]
10	250	1.4 (0.2)	8.3 (1.8)	0.85	0.10 (0.018)*
	10	1.2 (0.2)	8.6 (0.91)	0.52	0.061 (0.007)
35	250	2.7 (0.3)	14.1 (2.0)	1.0	0.074 (0.009)*
	10	2.6 (0.2)	13.0 (0.85)	0.78	0.060 (0.010)
100	250	5.9 (0.7)	17.9 (2.1)	1.1	0.062 (0.008)*
	10	6.8 (0.5	14.5 (1.1)	0.74	0.051 (0.008)

[a] Fraction of AVP excreted in urine unchanged [b] calculated from CL_R= Ae/D ● CL
* Statically significant impact of treatment (P< 0.05)

Changing the sodium diet from 250 meq/day to 10 meq/day decreased Ae/D of AVP statistically significantly. CL_R is expected to be also significantly decreased with the 10 meq/day diet. However, CL is not impacted because the contribution of CL_R to CL is ≤ 10%.

Study 2
The below table summarizes the mean CL, CL_R and steady-state concentrations of AVP in subjects in the presence and absence of furosemide:

Mean (SEM) Steady-State Plasma Concentrations, Total, Renal Clearances and Fraction of AVP Excreted Unchanged in Urine in Subjects in the Presence and Absence of Furosemide 40 mg iv.

Infusion Rate µU/kg/min	Furosemide	Css µU/mL	CL mL/kg/min	Ae/D	CL_R[a] mL/kg/min
10	no	1.1 (0.2)	11.0 (1.8)	0.099 (0.015)	1.1
	yes	1.2 (0.2)	9.6 (1.7)	0.078 (0.010)*	0.75
35	no	2.4 (0.2)	15.1 (1.8)	0.078 (0.010)	1.2
	yes	2.7 (0.2)	13.2 (1.1)	0.060 (0.007)*	0.79

[a] Calculated from the product of total clearance and fraction of AVP excreted in urine unchanged * Significant impact of treatment (P <0.05)

The presence of furosemide reduced the fraction of the dose excreted as unchanged AVP in urine significantly. However, furosemide had no impact on CL of AVP.

Study 3
The below table lists the relevant PK parameters of AVP in the presence and absence of infusions with ANP:

Mean (SEM) Steady-State Plasma Concentrations, Total, Renal Clearances and Fraction of AVP Excreted Unchanged in Urine with

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Subjects Receiving an AVP infusion at a rate of 35 μU/kg/min in the Presence and Absence of ANP Infusions of 20 or 40 μg/h

Infusion Rate μU/kg/min of ANP	ANP	Css μU/mL	CL mL/kg/min	Ae/D	CL_R[a] mL/kg/min	CL_R[a] mL/min
20	no	3.0 (0.2)	11.2 (0.73)	0.086 (0.012)	0.96	71 (9.0
	yes	2.9 (0.2)	11.2 (0.71)	0.109 (0.014)	1.22*	93 (10)*
40	no	2.9 (0.3)*	12.6 (1.5)	0.078(0.012)	0.98	68 (9.4)
	yes	2.5 (0.3)	15.0 (2.1)*	0.095 (0.009)	1.43*	101 (9.5)*

[a] Calculated from CL_R=Ae/D ● CL , where Ae is the amount of AVP excreted unchanged in urine and D is the dose *statistically significant impact of treatment with ANP (P<0.05)

In the presence of 40 μg ANP the steady-state plasma concentrations of AVP were statistically significantly greater than in the absence of ANP. The CL_R of AVP was significantly smaller in the presence of 20 and 40 μg ANP than in the absence of ANP. The CL of AVP was increased in the presence of 40 μg ANP.

PD

Study 1

The mean (SEM) osmolal clearance in the subjects placed on sodium diets of 250 meq/day or 10 meq/day and receiving different infusion rates of AVP is shown below:

Mean (SEM) Osmolal Clearance and Systolic and Diastolic Blood Pressure

Infusion Rate μU/kg/min	Sodium diet meq/day	Osmolal Clearance mL/min	Systolic BP mmHg	Diastolic BP mmHg
10	250	3.9 (0.43)*	125 (4)*	56 (5)
	10	1.7 (0.17)	117 (3)	57 (3)
35	250	3.2 (0.38)*	125 (3)*	56 (4)
	10	1.4 (0.18	122 (7)	61 (4)
100	250	2.5(0.30)*	124 (5)*	57 (4)
	10	1.4 (0.30)	116 (3)	57 (2)

* Treatment with 250 meq increased osmolal clearance and systolic BP statistically significantly

The 10 meq sodium/day diet reduced osmolal clearance and systolic BP statistically significantly compared to the treatment with a 250 meq sodium/day diet. Also urine flow with the 10 meq sodium diet/day was significantly decreased.

Study 2

Mean (SEM) Osmolal Clearance and Systolic and Diastolic Blood Pressure

Infusion Rate μU/kg/min	Furosemide	Osmolal Clearance mL/min	Systol. BP mmHg	Diastol. BP mmHg
10	no	3.6 (0.41)	122 (4)	70 (2)
	yes	22.4 (0.95)*	121 (3)	75 (4)*
35	no	3.0 (0.39)	122 (4)	67 (2)

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	yes	7.5 (0.69)*	122 (3)	75 (4)*

* statistically significantly greater in presence of furosemide (P <0.05)

In the presence of furosemide osmolal clearance was significantly greater and diastolic BP significantly smaller than in the absence of furosemide. Also the urine flow was significantly grater in the presence of furosemide.

Study 3

Mean (SEM) Osmolal Clearance and Systolic and Diastolic Blood Pressure In Subjects Receiving Infusions of AVP in the Presence of ANP Infused at 20 or 40 µU/kg/min

Infusion of µU/kg/min	Osmolal Clearance mL/min	Systolic BP mmHg	Diastolic BP mmHg
20 no	1.88 0.23)	114 (4)	70 (3)
20 yes	2.98 (0.43)*	115 (4)	68 (2)
40 no	1.72 (0.26)	115 (3)	67 (3)
40 yes	2.70 (0.40)*	117 (2)	68 (2)

* statistically significantly greater in presence of 20 or 40 µg ANP (P <0.05)

In the presence of ANP 20 µg or 40 µg the osmolal clearance was statistically significantly greater than in the absence of ANP. However, ANP infusions had no impact on systolic or diastolic BP. ANP also increased the urine flow significantly.

The respective ratios of the fraction of the dose excreted as unchanged AVP, osmolal clearance and urine flow with the test and reference treatments are listed in the below table:

Fold Change in PK and PD Parameters of AVP with Different Treatments

Comparison	AVP mU/min	Ratio of Ae/D	Ratio of CLosm	Ratio of Urine Flow
10/250 meq/day sodium	0.700	0.60	0.43	0.39
	2.45	0.81	0.45	0.45
	7.00	0.82	0.62	0.62
Furosemide/0	0.700	0.79	6.2	13.3
	2.45	0.76	2.5	5.1
20 APN/0	2.45	1.27	0.59	0.61
40 ANP/0	2.45	1.22	0.57	0.52

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

- The 3 treatments tested i.e. 10 meq/day sodium, co-administration of furosemide and ANP infusions do not impact the exposure to AVP, but they affect the fraction of the dose excreted as unchanged AVP as well as osmolar clearance and urine flow
- The 10mEq/day sodium diet is associated with an decreased fraction excreted unchanged in urine and renal clearance of AVP. Also, the osmolal clearance and

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systolic BP are smaller with the 10 meq/day diet compared to the 250 meq/day diet. • The presence of furosemide increases the fraction of unchanged AVP excreted in urine and the osmolal clearance significantly. Diastolic BP is significantly smaller in the presence of furosemide than in its absence. • In the presenc of 40 μg ANP the steady-state plasma concentrations of AVP are statistically significantly greater than in the absence of ANP. The CL_R of AVP is significantly greater in the presence of 20 and 40 μg ANP. The CL of AVP is increased in the presence of 40 μg ANP. The osmolal clearance in the presence of ANP is increased. • As in (1) the CL of AVP increases with increasing infusion rate • The CL and CL_R values of AVP in the present study in the absence of furosemide or ANP are similar to those in (1).
Comments
• None
References 1. Moses A and Steciak E. Urinary and metabolic clearances of arginine vasopressin in normal subjects. Am J Physiol 1986;251: R365-370

1.3

Report #	**Study Period**: Not indicated	**EDR Link:**
Title	Changes in Metabolic Clearance of Vasopressin and in Plasma Vasopressinase throughout Human Pregnancy. Davison JM, Sheills EA, Barron WM, Robinson AG, Lindheimer MD. J Clin Invest 1989; 83:1313-1318	
Study Design: Serial Intravenous infusions of AVP at different rates in 5 normotensive, healthy women before conception, between gestational weeks 7 and 8, 22 and 24, 36 and 38 (designated as early, mid- and late pregnancy), and again 10-12 weeks postpartum, when none was breast feeding or ingesting oral contraceptives to determine of the pharmacokinetics of AVP. In addition, 4 subjects, two women with a single kidney, one subject carrying twins and another subject carrying triplets, were studied, but only in late pregnancy and postpartum. They received only 2 infusions. Each study started at 9 A.M. with the volunteers seated comfortably. Control blood samples ere obtained and an infusion of normal saline (0.03mL/kg/min) was started after which the subjects drank 20 ml/kg tap water. Clearance measurements of AVP began 1 h later and after urine osmolality decreased below 100 mosmol/kg. Three AVP infusion rates, each preceded by a priming dose, were used during each test as shown in the below scheme:		

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Each infusion was maintained for 75 min, urine collected at 15 min intervals during he last 45 min, and blood samples obtained at 45, 60, and 75 min, respectively. Plasma osmolality was maintained at 270 mosmol/kg during pregnancy and 275 mosmol/kg mosmol/kg preconception and post-partum, by periodic ingestion of water. These osmolalities are expected to be low enough to ensure suppression of endogenous AVP release. To confirm this plasma neurophysin was determined in 3 of the 5 subjects on 15 occasions. The circulating levels of vasopressinase, a cystine-aminopeptidase enzyme, were monitored starting with the initial test, and then every 2-3 weeks until the postpartum study.

Rationale: A preliminary report has shown that the clearance of AVP is significantly increased during the third trimester	
Objectives: Primary: To determine the disposition of AVP at three different steady-state plasma concentrations of AVP	
Screening: Not indicated	**Washout:** None between the 3 AVP infusions administered prior to conception, during early, mid and late pregnancy and postpartum. Washout periods of 14 to 17 weeks and 12 to 16 weeks early, mid and late pregnancy, respectively. Several week washout between preconception and early pregnancy and late pregnancy and postpartum.
Periods	5
Treatment: 15 treatments consisting in a priming dose followed by a 75 min infusion, 3 treatments with ascending infusion rates on 5 occasions (see above dosing scheme)	
Sequence	Studies 1-5 each with 3 ascending prime doses and infusion rates
Dose Selection: See above dosing scheme	
Investigational Drugs and Formulations: AVP (Argipressin®, Parke-Davis, Detroit, Michigan)	
Administration: Intravenous	
Fed/Fasted: Not indicated	
Interfering Substances: Not indicated	
PK Sampling Times: Blood samples for determining the plasma concentrations of AVP, neurophysin were collected 45, 60 and 75 min into the infusions.	

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PD Sampling Times: Blood samples for the determination of plasma osmolality were collected 45, 60 and 75 minutes into the infusions. Urine volumes for the determination of urine osmolality were collected in the intervals 30-45, 45-60, and 60-75 min into the infusions.

Analytical Method

Analyte		AVP
Method		RIA
Matrix		Plasma
Range, ng/mL		Not indicated
Quality Control	%CV	Not indicated
	%RE	Not indicated

The blood for the determination of AVP was collected into syringes containing 0.1 mL phenanthroline (60mg/mL) solution and then rapidly added to chilled heparinized tubes, centrifuged in the cold, and extracted with acetone within 3 h of venipuncture. Highly purified ^{125}I AVP (biopotency 400 U/mg (Ferring Arzneimittel GmbH), Wittland FRG) and specific and sensitive antiserum were used to set up the standard curves. The antiserum showed cross-reactivity with lysine vasopressin (4.3%), arginine oxytocin (3.3%) and oxytocin <0.01%). The assay sensitivity is 0.1 pg/assay tube. Intra-assay coefficient of variation at medium (1-5 pg/mL), high (7.5 pg/mL) and low plasma concentrations< 1.0 pg/mLwere 9, 8 and 15%, respectively. The inter-assay coefficient of variation is 11-13%.

The plasma concentrations of neurophysin were measured by RIA. Plasma vasopressinase was measured by determining the rate of degradation of ^{125}I-AVP. Osmololality in plasma and urine was measured by freezing point depression methodology.

Target PK Parameters: Css, CL, Css was the mean of 3 concentrations of AVP after attainment of steady-state at 30, 45 and 60 min into the infusions

PK Data Analysis: CL=ko/CL. The baseline values reflecting endogenous AVP were not subtracted from Css. The tacit assumption was made that secretion of endogenous AVP would cease rapidly after initiation of the infusions with exogenous AVP so that AVP measured at 30, 45 and 60 min into the infusions would reflect only exogenous AVP.

Target PD Parameters: Plasma and urine osmolality

Statistical Method/Sample Size/Power: An analysis of variance (ANOVA) was performed to test whether the CL changes as a function of infusion rate in each of the 5 studies. From the significance of the F-ratio from this analysis, comparisons were performed using the t-test. Paired comparisons between test occasions were performed using the t-test. The sample size was not based on statistical considerations.

Results

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Study Population:

Randomized Treated Completed Discontinued Pharmacokinetic population Safety population	5 5 5 0 5 5
Age [Mean (SD)], years	Not indicated
Weight [Mean (SD)], kg	Not indicated
Male/Female	0/5
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated

In addition 4 female subjects completed treatments with 2 different infusion rates in late pregnancy and postpartum.

PK of AVP

The mean (SD) Css and CL (MCR, mL/min) of AVP, the plasma concentrations of neurophysin, and the plasma and urine osmolality determined in the 15 occasions are listed in the below table:

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The pre-dose plasma concentrations of AVP (P_{AVP}) ranged between 0.7 and 1.2 pg/mL. The pre-dose neurophysin levels ($P_{neurophysin}$) decreased from pre-dose levels of 0.74-0.94 ng/mL to < 0.5 ng/mL during the tests indicating that the water loading suppressed release of endogenous AVP. Plasma osmolality (Posmol) during the tests was in the targeted range. The steady-state plasma concentrations of AVP showed a coefficient of variation ranging between about 46 and 62%. The mean CL of AVP (MCR_{AVP}) was independent of the infusion rate when the rate was increased 3 fold at all 5 test occasions, but increased significantly from preconception with 767 mL/min to 935, 2869, and 3116 mL/min as pregnancy progressed and returned to 709 mL/min postpartum back to the preconception values. The greatest change took place between gestational weeks 6 and 8 and 22 and 24.

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The CL values for 2 women with a single kidney and those carrying twins and triplets are shown in the below table:

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The data in these 4 women are not incompatible with those in the 5 women of the main study.

The below table lists the mean CL of AVP expressed in mL in the 5 women tested during 5 occasions before, during and after pregnancy for easier comparison of the results obtained in other publications:

Mean (SD) Clearance of AVP in Healthy Women Before During and after Pregnancy

Infusion Rate	Time	CL
pg/kg/min	weeks	mLmin
24, 48, 72	Preconception	767 (11.0)
24, 48, 72	7-8 (Early Pregnancy)	935 (13.6)
84, 144, 246	22-24 (Mid Pregnancy)	2869 (41.0)
84, 144, 246	36-38 (Late Pregnancy)	3116 (44.5)
24, 42, 72	Postpartum	709 (10.1)

The mean baseline concentrations of AVP before, during and after pregnancy ranging between 0.7-1.1 pg/mL were comparable. Assuming that the baseline concentrations represent endogenous AVP at steady-state the mean secretion rates of endogenous AVP calculated from $ko_{,endog} = CL \bullet C_{baseline}$ where CL is identical for endogenous and endogenous AVP. The respective secretion rates are 690, 748, 2008, 3116 and 780 pg/min prior to conception, in early, mid and late pregnancy and postpartum, respectively, indicating a gradual increase in secretion of endogenous AVP to compensate for the increased disposition during pregnancy.

Vasopressinase Levels

The plasma vasopressinase levels showed a time profile similar to the CL of AVP as shown in the below figure:

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Figure 3. Plasma vasopressinase activity measured serially in the five women who underwent the metabolic clearance studies. Measurements of $P_{vasopressinase}$ started before conception and were repeated at 2–3-wk intervals until postpartum weeks 10–12. Two indices were used, one derived from the rapidity by which the enzyme degraded ^{125}I-AVP tracer (*vertical lines*) and the other by photometry using 5-benzyl-L-cystine-*p*-nitroanilide as substrate (*speckled area*). Solid and dashed lines enclosing the vertical lines and speckled area represent ±1 SD.

The % initial immunoreactivity read off from Figure 3 indicate the following mean values during early, mid and late pregnancy is 2.7, 40 and 56, respectively, suggesting an about 20 fold increase of the vasopressinase activity during pregnancy.
The authors' conclude that increased activity of vasopressinase is responsible for the observed significant increases in CL of AVP during pregnancy. The placenta is known to contain significant amounts of vasopressinase. The trophoblastic mass increases 1000 fold between gestational weeks 6 and 24. Alternatively, an increase in renal blood flow (30-50%) and hepatic blood flow (controversial) in pregnancy could be responsible for the observed increase in the CL of AVP. However, the increase in renal blood flow occurs early in pregnancy at a time when CL of AVP is not importantly increased. Also, the women with the single kidneys showed an increase in the CL of AVP during their late pregnancy similar to that of healthy gravidae. The Reviewer agrees that the vasopressinase hypothesis is more plausible than the increased blood flow hypothesis.

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

- The CL of exogenous AVP increases 4 to 5 fold during the course of pregnancy with peaking during the last trimester of pregnancy
- The CL of exogenous AVP does not change when the prime dose and the constant infusion rate are increased 3 fold before, during or after pregnancy
- The constancy of the pre-dose AVP concentrations preconception, throughout pregnancy and postpartum indicates that the production rate of endogenous vasopressin increases gradually during pregnancy to compensate for the increased disposition caused by circulating vasopressinase.

Comments

- None

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1.4

Report #	Study Period: Not indicated	EDR Link
Title	Distribution, Blood Transport, and Degradation of Antidiuretic Hormone in Man. Baumann G, Dingman JF. J Clin Invest 1976;57:1109-1116	

Study Design: Single group study in 10 healthy, hydrated subjects (oral water load of 20 mL/kg 90 min before injection). The subjects received 10 drops of potassium iodide to block thyroidal uptake of iodine prior to the injection of radio-labeled AVP. ^{131}I albumin was injected prior to or simultaneously with ^{125}I-AVP to measure plasma volume and "mixing time".

Rationale: The results obtained on antidiuretic hormone (ADH) with bioassays have shown controversial results. The information available on the metabolism of ADH is limited.

Objectives: Primary: To investigate the metabolism of AVP at physiological concentrations in man

Endpoints: Distribution and metabolic clearance of AVP, urine flow and urine osmolality

Screening: Not indicated	**Washout:** Not applicable

Periods	Not applicable

Treatment: Intravenous bolus of ^{125}I-AVP

Sequence	Not applicable

Dose Selection: 2-7 μCi **(**9.5-99 ng) ^{125} I-AVP

Investigational Drugs and Formulations: Mono-iodinated synthetic AVP (Sandoz Ltd, Basel, Switzerland) with a specific bioactivity of 470 U/mg when assayed against USP bovine posterior pituitary standard. The position, purity and biological activity of the radio-labeled AVP are not indicated in the publication

Administration: Intravenous bolus

Fed/Fasted: Fed

Interfering Substances: Not indicated

PK Sampling Times: Frequent blood samples were collected over 60 min after injection, Voided urine was collected at 10, 20, 30, 45 and 60 min after injection

PD Sampling Times: 10, 20, 30, 45 and 60 min after injection

Analytical Method

PK

Analyte		AVP and Metabolites
Method		AVP
Matrix		Plasma
Range, ng/mL		Not indicated
Quality Control	%CV	Not indicated
	%RE	Not indicated

Blood was chilled immediately to 0 C after collection. Radioactivity in plasma and urine was measured by dual-channel gamma spectrometry. Radioactivity in red blood cells, measured in samples collected up to 20 min after injection, was obtained after washing with isosaline. Binding of ^{125}I-AVP was measured at 37 C in vitro and at 4 C ex vivo by gel chromatography. The peptidase inhibitor trasylol was added to 50% of the samples. Intact ^{125}I-AVP was determined by ascending chromatography on silicic-impregnated glass

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paper using the slow and fast solving system n-butanol: acetic acid: water=8:2:3). Metabolites of AVP in urine were determined by the same system chromatography without prior extraction. Metabolites in plasma were determined after precipitation of the proteins with trichloro- acetic acid and subsequent extraction of the supernatant with diethylether and, after evaporation to a small volume, by chromatograpy with the above system.

PD
Osmolality in urine was measured by freezing point depression

Target PK Parameters: CL, CL_R, V_D, t1/2; CL, V_D and t1/2 were derived from the plasma concentrations of chromatographically intact ^{125}I-AVP considering plasma concentrations from 6-20 min. Approximate CL_R was determined from the excretion rate of total radioactivity excreted in urine divided by the mean plasma concentration of plasma radioactivity.

PK Data Analysis: Compartment model independent methods

Target PD Parameters: Urine osmolality

Statistical Method: Not indicated
Sample Size/Power: The selected sample size is not based on power considerations.

Results

Study Population:

Age [Range], years	20-29
Weight [Mean (SD)], kg	Not indicated
Male/Female	5/5
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated

PK
The recovery of the administered total radioactivity in urine up to 24 h after injection ranged between 78 and 100% in the 8 subjects in whom the recovery was indicated in the publication. The disappearance curve of the logarithmically transformed chromatographically intact ^{125}I-AVP concentrations against time is shown below:

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The mean (SEM) apparent terminal disposition phase measured form the concentrations meaured between 10 and 20 min was 24 min. Mean (SEM) CL was 4.1 (0.27) mL/min and V_D was 141 (7.9) mL/kg/min. Approximate mean CL_R was 1.1 (0.26) mL/min.

No evidence for plasma protein binding or red cell partitioning/binding of ^{125}I-AVP was found. Trasyslol appeared to inhibit the breakdown of ^{125}I-AVP.
Metabolites of ^{125}I AVP were found in plasma (up to 16% of total radioactivity) and urine.

PD
Doses between 9.5 to 25 ng of ^{125}I-AVP had no consistent impact on either urine flow (7-15 mL/min) or urine osmolality (< 100 mosmol/kg).

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

PK

- 78-100% of the administered total radioactivity is recovered in urine as parent drug or metabolites within 24 h after administration indicating rapid disposition of ^{125}I-AVP. There appears no be no significant biliary excretion of ^{125}I-AVP or metabolites.

Limitations of the study precluding additional conclusions include:

- Labeling of AVP with ^{125}I may alter the biological properties of AVP
- Purity, label location and biological activity of the injected ^{125}I-AVP and the recovery of intact ^{125}I-AVP in urine are not reported
- The estimated approximate renal clearance does not represent the true CL_R of ^{125}I-AVP
- The red cells were washed before total radioactivity was measured, therefore the conclusion that ^{125}I AVP does not distribute into the red cells may not be correct

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• The t1/2 of 24 min estimated from a too short 10 min segment of the log linear time curve is likely biased
Comments
• None

2. Dose/Exposure-Response: Healthy Adults & Drager-Shy Syndrome

2.1

Report #	**Study Period**: Not indicated	**EDR Link**
Title	The Pressor Effect of the Antidiuretic Principle of the Posterior Pituitary in Orthostatic Hypotension. Wagner HH, Braunwald E. J Clin Invest 1956;35:1412-1418	
Focus of Review	The review focuses on the dose-response relationship of purified vasopressin Pitressin®	
Study Design: Three parallel groups were investigated. The first group consisted of 6 young healthy subjects. The second group consisted of 8 healthy subjects. The third group consisted of 3 patients with idiopathic orthostatic hypotension. In a fourth group subjects without symptoms of hypotension received intravenous injections of the ganglionic blocker tetraethylammonium (TEA). The first group of 6 healthy subjects received intravenous infusions of 120 min and single intravenous injections of Pitressin ®. The second group of 8 healthy subjects received single intravenous injections of Pitressin®. The 3 patients of Group 3 with idiopathic orthostatic hypotension received intravenous Pitressin® or highly purified vasopressin injections. Cardiac output (CO), total systemic vascular resistance (SVR) and the renal effects of Pitressin ® including para-aminohippurate (PAH)- and inulin clearance (GFR) and filtration fractions were determined in 1or 2 of the 3 patients. The fourth group of subjects without symptoms of orthostatic hypotension received intravenous injections of Pitressin ® in the presence and absence of TEA.		
Rationale: posterior pituitary extracts exert pressure effects in anesthetized and spinal animals, but demonstration of a pressor effect in man has not been possible thus far		
Objectives: Primary: to investigate the pressor effect of posterior pituitary hormones in 6 healthy subjects and 3 patients with idiopathic hypotension.		
Endpoints: Systolic, diastolic blood pressure (SBP, DBP), mean arterial pressure (MAP), cardiac output (CO), pulmonary artery pressure (PAP), right atrial pressure effective, systemic vascular resistance, SVR, renal plasma flow (EPF) by PAH clearance, glomerular filtration rate (GFR) by clearance of inulin.		
Inclusion Criteria: Patients with hypotension, hypohidrosis, and impotence, passive tilting in head-up position > 45 degrees resulted in syncope and BP unobtainable by sphygmomanometry		
Exclusion Criteria: Not indicated		
Screening: Not indicated	**Washout:** Not applicable	
Periods	Not applicable	
Treatment: Healthy subjects received an infusions and injections of Pitressin®. During control studies on another day, an equal volume of saline was infused. Patients with		

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idiopathic orthostatic hypotension received intravenous injections of Pitressin® in presence an absence of TEA.	
Sequence	Not applicable
Dose Selection: Intravenous infusion of 0.0567 U/min to 0.262 U/min in healthy subjects, Intravenous injections of 0.5 or 1.0 U in healthy subjects, injections of 0.01, 0.10, 1.0 U in patients with idiopathic orthostatic hypertension, and intravenous injection of 0.5 U in presence and absence of 300-400 mg TEA	
Investigational Drugs and Formulations: Pitressin®, highly purified vsopressin	
Administration: Intravenous infusion and injections	
Fed/Fasted: Not indicated	
Interfering Substances: Not indicated	
PK Sampling Times: No blood samples for the determination of AVP were collected.	
PD Sampling Times: Blood pressure recorded for 5-20 min after administration of Pitressin®	
Analytical Method: No blood samples for the determination of VAP were collected	
Target PK Parameters: Not applicable	
PK Data Analysis: Not applicable	
Target PD Parameters: SBP, DBP (by sphygmomanometry except in acute studies where BP was recorded through an indwelling brachial or femoral arterial needle), cardiac index, pulmonary arterial pressure	
Statistical Method: Not indicated	
Results	

Study Population:

Group 1 Healthy Subject	
Treated	6
Completed	6
Discontinued: withdrawal from study at request of subject	0
Pharmacodynamic population	6
Safety population	6
Group 2 subjects	
Treated	8
Completed	8
Discontinued: withdrawal from study at request of subject	0
Pharmacodnamic population	8
Safety population	8
Group 3 patients with idiopathic orthostatic hypotension	
Treated	3
Completed	3
Discontinued: withdrawal from study at request of subject	0
Pharmacodynamic population	3
Safety population	3
Group 4 subjects without orthostatic hypotension	
Treated	4

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Completed Discontinued: withdrawal from study at request of subject Pharmacodnamic population Safety population	4 0 4 4
Age [Range], years healthy subjects	18-21
Patients	55-66
Weight [Mean (SD)], kg	Not indicated
Male/Female healthy Subjects	Not indicated
Patients	3/0
Race (Caucasian/Black/Hispanic/ Asian/Other) healthy Subjects	Not indicated
Patients	3/0/0/0

PD

Group 1 Healthy Subjects
Intravenous infusions of Pitressin® 0.0567 and 0.262 U/min for 2 h had no significant effect on the arterial pressures in the healthy subjects. Single intravenous injections of 500 or 1000 U Pitressin® resulted in a transient increase of the SBP and DBP of 18 and 15 mm Hg, respectively.

Group 2 Healthy Subjects

Single intravenous injections of 0.5 or 1.0 U of Pitressin® resulted in a transient elevation of the systolic and diastolic blood pressure of 18 and 15 mm Hg, respectively, lasting 3-5 min.

Group 3 Patients with Idiopathic Orthostatic Hypotension
After intravenous injections of 0.010, 0.1 and 1.0 U highly purified vasopressin dose dependent increases of SBP (14,42,76 mmHg) and DBP (7, 26, 52 mm Hg) are observed as shown below:

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The pressor effect on BP occurred in the patients at much lower doses of vasopressin than in the healthy young subjects after Pitressin®. Two (2) of the 3 patients exhibited significant elevations of BP already when vasopressin was infused at a rate of 1 mU/min or following a single intravenous injection of 10 mU.
The impact of vasopressin on the hemodynamic variables in 2 of the 3 patients is shown in the below table:

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A trend for an increase in SVR and PAP was observed in the patients after infusions of vasopressin.

Group 4 Subjects without Orthostatic Hypotension

Intravenous bolus administration of Pitressin® 500 mU did not increase SBP and DBP in the 20 min postinjection interval in the subjects. However, the same dose of Pitressin® increased median SBP and DBP by 32 and 26 Hg, respectively, after intravenous pretreatment with 300-400 mg of the ganglion blocking agent tetraethylammonium (TEA) in 4 subjects as shown in the below table:

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Administration of the same dose of TEA alone had no effect on SBP and DBP in the subjects without orthostatic hypotension.

The below table lists the changes in MAP after Pitressin® alone, Pitressin® after administration of TEA and the fold increase in MAP when Pitressin® is administered after TEA:

	MAP		
Subject	Pitressin 0.500 U	Pitressin 0.500 U + TEA 0.3-0.4 g	Fold increase in presence and absence of TEA
YS	101	125	1.24
GE	98	114	1.16
MG	105	123	1.17

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MU	110	149	1.35

MAP was calculated by the Reviewer from the systolic and diastolic blood pressures (SBP, DBP) using the equation MAP=DB +1/3 (SBP-DB)

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

PD

- Healthy Subjects

Intravenous infusions of up to 0.262 U/min have no effect on the BP. Single intravenous injections >500 mU/min Pitressin® are required to increase BP transiently (5min).

- Patients with Idiopathic Orthostatic Hypotension

After intravenous injections of 0.010, 0.1 and 1.0 U highly purified vasopressin dose dependent increases of SBP (14,42,76 mmHg) and DBP (7,26, 52 mm Hg) are observed indicating a sharply increased sensitivity to the pressor effects of Pitressin®.

- Subjects without Orthostatic Hypotension

Intravenous injection of 0.5 U Pitressin® after pretreatment with TEA increases the mean MAP between 1.2 to 1.4 fold.

Comments

- None

2.2

Report #	**Study Period:** Not indicated	**EDR Link**
Title	Greatly Enhanced Pressor Response to Antidiuretic Hormone in Patients with Impaired Cardiovascular Reflexes Due to Idiopathic Orthostatic Hypotension. Moehring J, Glaenzer K, Maciel J A Jr, Duesing R, Kramer HJ, Arbogast R, Koch-Weser J. J Cardiovasc Pharmacol 1980; 2:367-376	

Study Design: Parallel group study of patients with idiopathic hypotension and in healthy subjects with sequential infusions given at 4 different infusion rates. The impact of exogenous AVP infusions on exposure and hemodyamic response were investigated in 2 patients with idiopathic hypotension or Shy-Drager‘s syndrome and 3 healthy male subjects. Another 8 healthy subjects participated in the noradrenaline and angiotensin II infusion studies. The diagnosis in the patients was based on conventional criteria, including precipitous fall of blood pressure (BP) with no change in heart rate (HR) during orthostasis, lack of typical BP and HR changes during Valsalva’s maneuver, and no change of BP or HR during noise or mental arithmetics. The studies were performed in the morning or early afternoon. Subjects were investigated in the recumbent position. Isotonic saline or AVP was infused intravenously via an indwelling cannula. Venous blood was sampled form another cannula. BP and HR was recorded every two min. BP and HR stabilized after 1-2 h rest and infusion of isotonic saline (about 50 mL/h). Each dose of AVP was infused over 20 min with intervals of 20-30 min between infusions. The 3 healthy volunteers received AVP at infusion rates of 8.0, 38.4, 160 and 416 pmol/min (3.2, 15.4, 64, and 166 mU/min), respectively. The 2 patients received AVP

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at 5 times lower infusion rates of 1.60, 7.76, 32.0, 83.2 mU/min (0.64, 3.08, 12.8, 33.2 mU/min). In the 2 patients and in 8 control subjects doses of noradrenaline (Arterenol®, Hoechst) and angiotensin II (Hypertensin®, Ciba) which increased BP by 10 and 20 mm Hg during a 10 min infusion period were determined according to the principles of the Kaplan test.

Rationale: Wagner and Braunwald (1) reported that the BP of patients with idiopathic orthostatic hypotension with reduced cardiovascular reflex activity is raised 25 to 50 mmHg by an infusion of 1 or 3 mU/min of vasopressin, whereas an infusion of up to 260 mU/min into normal subjects does not significantly increase BP.

Objectives: Primary: To compare the partial dose-response curves for AVP, noradrenaline, or angiotensin II infused into 2 patients with idiopathic orthostatic hypotension with those obtained in normal subjects. In the AVP infusion studies the plasma concentrations of AVP were measured**.**

Screening: Not indicated	**Washout:** 20-30 min
Periods	Not applicable

Treatment: Intravenous infusions of AVP

Sequence	Not applicable

Dose Selection: Earlier studies have shown that patients with orthostatic hypotension tolerate rates of 20 U/min Pitressin® (extract from the posterior pituitary). Because of the known increased sensitivity of patients with idiopathic orthostatic hypotension for pressor drugs the infusion rates of AVP were set about 5 fold lower than for those for the healthy subjects.

Investigational Drugs and Formulations: Synthetic AVP (Ferring, Malmoe, Sweden)

Administration: Intravenous infusions

Fed/Fasted: Studies were performed after ingestion of a light breakfast or lunch

Interfering Substances: Not indicated

PK Sampling Times: Pre-dose ($C_{baseline}$) and 20 min after constant infusion of AVP (C_{20})

PD Sampling Times: Mean arterial BP (MAP) and HR were measured every 2 minutes for the duration of the AVP infusions

Analytical Method

Analyte		AVP
Method		RIA
Matrix		Plasma
Range, ng/mL		Not indicated
Quality Control	%CV	Not indicated
	%RE	Not indicated

The reference (2) given describes an RIA for determining AVP in rat plasma not human plasma. However, there was a highly significant correlation between plasma samples in humans measured by the authors' RIA and different RIA whose performance passes the acceptance criteria (3).

Target PK Parameters: Pre-dose concentration and concentration after 20 min of infusion with AVP

PK Data Analysis: None

Target PD Parameters: MAP was calculated from systolic and diastolic BP in the conventional way. The mean increase of MAP represents the difference between the last 3 BP

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values of the 20 min infusion periods and the pre-and post-infusion base-line values.

Statistical Method/Sample Size/Power: The significance of a difference between means was estimated by the t-test for paired data. Regression equations were obtained by the method of least squares. The selected sample sizes for the 3 groups investigated are not based on power considerations.

Results

Study Population:

Enrolled Treated Completed Discontinued PK-PD population Safety population	2 patients with Shy-Drager's syndrome, 3 healthy subjects 5 5 0 5 5
Age [Mean (SD)], years	2 patients of 70 and 58 years, 3 healthy subjects of 38, 38 and 39 years
Weight [Mean (SD)], kg	2 patients of 66 and 70 kg 3 healthy subjects of 72, 68 and 75 kg
Male/Female	1 female and 1 male patients, 3 male healthy subjects
Race (White/Black/Hispanic/ Asian/Other)	Not indicated

Exposure-Response Relationship

The below plots of the increase in MAP vs. the logarithm of the plasma concentrations of AVP indicate a linear relationship with a flat slope in healthy subjects (Δ BP=2.7 • log C- 0.1) and much steeper slopes in the patients with idiopathic orthostatic hypotension:

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The increase in MAP in the patients with idiopathic orthostatic hypotension was much greater than in the healthy subjects even though the infusion rates of AVP were 5 fold smaller indicating an increased sensitivity of the patients to AVP.

The control AVP concentrations were 4.6, 3.5 and 11.2 fmol/mL in the 3 subjects.

The relationship between infusion rate and MAP in the healthy subjects and patients with idiopathic orthostatic hypotension enrolled in the present study and the 3 patients with idiopathic orthostatic hypotension studied earlier by Wagner & Braunwald (1) shown in the below figure confirm the significantly greater sensitivity of the patients to the pressor effects of AVP:

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Effects of AVP on MAP and Heart Rate

Healthy Subjects

The baseline mean (SEM) MAP and HR were 90 (0.7), 109 (1.2) and 80 (1.2) mm Hg and 64 (1.2), 75 (0.9) and 70 (1.2) bpm in the 3 healthy subjects. After the 20 min infusions of the three highest doses of AVP (about 0.50, 2.1 and 6.2 pmol/kg/min), diastolic, systolic and MAP increased significantly. During infusion of the smallest dose (about 0.10 pmol/kg/min) MAP did not change significantly, although a slight increase was calculated in each case.

The below figures show the effect of AVP infusions at a rate of 5.8 and 2.4 pmol/kg/min on MAP and HR in 2 of the 3 healthy subjects:

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In both subjects the mean BP blood pressure increased within a few minutes after start of the 20 min AVP infusions and reached a transient peak effect within 10-15 min. Thereafter, the MAP decreased without reaching the baseline value at the end of the 20 minute infusion. The HR decreased for the first 10 min and then increased over the remainder of the 20 min infusion interval. After infusion stop MAP and HR reached the respective baseline values within 10 min.

Patients with Idiopathic Orthostatic Hypotension

Reference ID: 3313815

The below figures show mean MAP and HR after about 20 min infusion rates of 0.024 pmol/kg/min in patients EF and 1.1 pmol/kg/min in patient RS with idiopathic orthostatic hypotension:

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In patient EF the baseline mean (SEM) MAP [93(1.4) mm Hg] was more variable than in the healthy subjects and in patient RS [86 (0.6) mmHg], whereas the HR at baseline in both patients [patient EF: 94 (0.3) bpm, patient RS: 59 (0.2) bpm] was constant during the control period. In patient EF infusion of AVP at the smallest rate of 0.024 pmol/kg/min, after a short delay, caused a rise in MAP over the entire 24 min infusion interval. The HR remained unchanged throughout the infusion of 0.024 pmol/kg/min. After infusion of AVP in patient EF at the next higher next rate of 0.12 pmol/kg/min, systolic BP fluctuated between 175 and 185

Reference ID: 3313815

mm Hg and remained in that range, while diastolic BP fluctuated between 100 and 140 mmHg. During the first 3 min of an infusion of 0.49 pmol/kg/min AVP diastolic BP in patient EF surpassed 150 mm Hg, and the infusion was immediately stopped. During AVP infusion mean MAP in patients RS reached a plateau within 5-10 min which was maintained until the infusion stop. HR remained unchanged throughout the 20 min infusion. In both patients MAP and HR approached baseline within 10 minutes after infusion stop.

Infusion of Noradrenalin and Angiotensin II

The doses of noradrenaline and angiotensin II which increased MAP by 10-20 mmHg are listed in the below table:

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The results indicate that the two patients with idiopathic orthostatic hypotension needed 2-10 times smaller doses to attain the required increments in MAP.

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- At the two highest infusion rates of AVP the healthy subjects exhibited pallor and two of the 3 mentioned an urge to defecate.

Conclusion

- Plots of the increase in MAP vs. the logarithm of the plasma concentrations of AVP indicate an apparent linear relationship with a flat slope in healthy subjects and a much steeper slope in the patients. These findings suggest a largely increased sensitivity for the pressor activity of AVP in the patients with idiopathic orthostatic hypotension.
- AVP appears to exert only an effect on MAP in the patients with orthostatic hypotension whereas in healthy subjects AVP impacts MAP and HR.
- The onset of the MAP effect occurs in the first 10 min after infusion start in healthy subjects and patients with idiopathic orthostatic hypotension. Peak effects on MAP are observed in healthy subjects by 10-15 min of infusion initiation. Thereafter the effect on MAP fades. in the patients with idiopathic orthostatic hypotension the time to peak effect is more variable and the duration of the effect is ≥ 20 min. Offset of the effects on MAP and HR in healthy subjects and o MAP in the patients with idiopathic hypotension occurs within 10 min after infusion stop.
- The changes in HR are the mirror image of the changes in MAP in healthy subjects,

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whereas AVP does not impact heart rate in the patients with idiopathic orthostatic hypotension. The offset of the effect of AVP on MAP and HR occurs within 10 min after stopping the infusion in healthy subjects. In the patients with idiopathic orthostatic hypotension the offset of effect on MAP occurs within 10 min of stopping the infusion. • Pallor and urge for defecation was observed at the two highest infusion rates of AVP in the healthy subjects Limitations of the study • The specifics on the RIA method when used in human plasma and its performance are not provided.
Comments
• None
References 1. Wagner HN, Braunwald E. The pressor effect of the antidiuretic principle of the posterior pituitary in orthostatic hypotension. J Clin Invet1956;35: 1412-1418 2. Moehring B and Moehring J. Plasma ADH in normal Long-Evans rats and in Long-Evans rats heterozygous and homozygous for hypothalamic diabetes insipidus. Life Sciences 1975; 1307-1314 3. Glaenzer K, Appenheimer, Krueck F, Vetter W, Vetter H. Measurement of 8-arginine vasopressin by radioimmunoassay. Acta Endocrinologica 1984; 106, 317-329

2.3

Report #	**Study Period**: Not indicated	**EDR Link**
Title	Hemodynamic and Hormonal Responses to 8-Arginine-Vasopressin in Healthy Man: Effects of Indomethacin. Glänzer K, Prüssing B, Düsing R, Kramer HJ. Klin Wochenschrift.1982; 60:1234-1239	
Study Design: Single group study in 7 healthy subjects. After a control period of 60 min AVP was infused at a constant rate over a period of 60 min and a second control period of 60 min followed. In 4 of the 7 subjects the same protocol was repeated after the volunteers were pretreated with indomethacin 100 mg given orally the evening before and 100 mg 3 h before the study.		
Rationale: Thus far detailed hemodynamic data on stroke volume and cardiac output during AVP infusion in healthy subjects have not been reported.		
Objectives: Primary: to investigate the role of endogenous hormones and their relationship to hemodynamic changes. Plasma renin activity during AVP infusion and the impact of the prostaglandin inhibitor indomethacin pretreatment were determined.		
Endpoints: Systolic, diastolic blood pressure (ABP, DBP), mean arterial blood pressure (DBP+(SBP-DBP) ● 0.43, cardiac index (CI), heart rate (F), stroke volume SV (impedance cardiography), total peripheral resistance index (TPRI)		
Inclusion Criteria: Stable water and electrolyte balance with excretion of 170 mmol sodium and 60-70 mmol potassium per day		
Exclusion Criteria: Not indicated		
Screening: Not indicated	**Washout:** Not indicated	
Periods	Not applicable	

Reference ID: 3313815

Treatment: Infusion of AVP and infusion of AVP after pretreatment with indomethacin	
Sequence	Not applicable
Dose Selection: 160 pmol/min for 60 min corresponding to 173440 pg/min	
Investigational Drugs and Formulations: AVP (Ferring AB, Kiel)	
Administration: Intravenous infusion	
Fed/Fasted: Intake of standardized continental breakfast at home prior to study start	
Interfering Substances: Not indicated	
PK and PD Sampling Times: 10, 20, 30 60 min after initiation of the AVP infusion and 20, 40 and 60 min after infusion stop	

Analytical Method

Analyte		AVP
Method		RIA
Matrix		Plasma
Range, ng/mL		Not indicated
Quality Control	%CV	Not indicated
	%RE	Not indicated

Blood samples were taken into to pre-cooled, evacuated glass tubes, centrifuged at 4 ˚ C and deep frozen at -30 ˚ C until assaying. The plasma samples were acidified, extracted using octadecasilyl-treated silica packed in small columns (C18 Sep-Paks), and eluted with acetonitril. The recovery of AVP in spiked plasma was 88%. The limit of detectability was 0.3 pg/tube. The inter-assay and intra-assay coefficients of variation in plasma were 4.9% and 12.4%, respectively

The specificity of the assay for AVP showed the following relative displacement factors of AVP in the presence of structurally related compounds: LVP 17%, oxytocin 0.04%, dDAVP 0.32%. The plasma concentrations were measured by the methods of Moehring & Moehring (1) and Glaenzer et al. (2). The correlation coefficient between the 2 assays was 0.98.

Plasma renin activity (PRA) was determined by RIA.

The publication does not indicate whether the reported plasma concentrations were obtained with the method by Moehring & Moehring or Glaenzer et al. (1,2)

Target PK Parameters: CL, t1/2 and V_{ss}

PK Data Analysis: Non-compartmental, one compartment model

Target PD Parameters: SBP, DBP, MAP, F, SV, CI, TPRI

Statistical Method/Sample Size/Power: The T-test was used for paired data or Wilcoxon's matched pairs rank sign test. The selected sample size is not based on power considerations.

Results

Reference ID: 3313815

Study Population:

Treated Completed Discontinued Pharmacodynamic/Pharmacokinetic population Safety population	7 7 0 7 7
Age [Range)], years	22-27
Weight [Mean (SD)], kg	Not indicated
Male/Female	4/3
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated

The below table lists the mean (SEM) hemodynamic and hormonal variables:

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PD

The impact of AVP on the hemodynamic variables and PRA are shown in the below figure:

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The mean change from baseline in the hemodynamic variables and PRA during and after infusion of AVP is shown with and without pretreatment of indomethacin. Means (SEM) are shown for the PRA and AVP concentrations. The mean plasma concentration of AVP increases up to 60 min after initiation of the infusion. After infusion stop the concentration declines rapidly. In the absence of indomethacin a statistically significant transient increase in TPR (+29%) and decreases in F (-15%) and CO (-19%) are observed. The onset of the changes in the hemodynamic variables occurs within 4-10 min after initiation of the infusion. No significant change in MAP is observed. Ten (10) min after start SV and CO are still statistically significantly decreased. Twenty (20) min after start of the AVP infusion all hemodynamic variables return to the baseline.

Pre-treatment with indomethacin increases significantly TPRI at baseline (+42%).
After 8 min of AVP infusion F decreases by 21%, and SV 10% resulting in a 30% reduction of CO. In the presence of indomethacin the AVP infusion increases TRPI (+33%).The

Reference ID: 3313815

increase in TRPI and decrease in CO last throughout the AVP infusion and post-infusion periods. Indomethacin pre-treatment also inhibits significantly PRA.

PK

The estimates for CL, Vss, MRT, V_D and t1/2 of AVP by non-compartmental and one-compartment model analyses are listed in the below table:

Model	CL	Vss	t1/2
	mL/min	L	min
1-compartment	765	11.2	10

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- Immediately after infusion start the healthy subjects developed a marked pallor which persisted until the end of the infusion period. No other adverse events, especially no ST-segment depression

Conclusion

PK

- Mean CL, V_{SS}, and t1/2 of AVP are 765 mL/min, 11.2 L and 10 min, respectively, after infusion of AVP at a rate of 173.4 ng/min.

PD

- Transient increases in TPRI (+29%) and reductions in F (-15%), CO (-19%) are observed. The onset of the changes in the hemodynamic variables occurs within 4-10 min after initiation of the infusion. Twenty (20) min after start of the AVP infusion all hemodynamic variables return to the baseline.
- Pre-treatment with indomethacin increases significantly TRPI at baseline (+42%). After 8 min of AVP infusion F decreases by 21%, and SV 10% resulting in a 30% reduction of CO. In the presence of indomethacin the AVP infusion increases TRPI (+33%).The increase in TRPI and decrease in CO last throughout the AVP infusion and post-infusion periods. Indomethacin pre-treatment also inhibits significantly PRA.

Safety

- All subjects showed marked pallor staring with the imitation of the AVP infusion and lasting throughout the entire infusion period.

Comments

- None

References

1. Moehring B and Moehring J. Plasma ADH in normal Long-Evans rats and in Long-Evans rats heterozygous and homozygous for hypothalamic diabetes insipidus. Life Sci 1975;17: 1307-1314
2. Glaenzer K, Appenheimer M, Krueck F, Vetter W, Vetter H. Measurement of 8-arginine -vasopressin by radioimmunoassay. Development and application to urine and plasma samples using one extraction method. Acta Endocrinologica 1984;106:317-329

Reference ID: 3313815

2.4

Report #	**Study Period:** Not indicated	**EDR Link**
Title	Release of Prolactin as well as Adrenocorticotropin after Administration of Arginine-Vasopressin to Healthy Men. Erfurth E, Hedner P, Lundin S, Ekman R. Horm Metab Res 1996;28:602	
Study Design: Single blind, randomized, crossover, two-period, two-treatment study with administration of AVP and saline. Subjects arrived at Unit at 8 AM. After resting for 30 min in the supine position they received an intravenous bolus injection of AVP or saline.		
Rationale: AVP impacts ACTH. However, AVP's impact on the other pituitary hormones is less clear. Some reports have shown that AVP can impact the level of other pituitary hormones, other reports have not.		
Inclusion Criteria: Healthy subjects males, non smokers		
Objectives: Primary: Using a controlled study approach to clarify this issue.		
Screening: Not indicated	**Washout:** ≥ 1 week	
Periods	2	
Treatments: AVP or saline intravenous bolus injection		
Sequence	Randomized crossover	
Dose Selection: AVP given at the some dose in pa previous study by the same author increased cortisone level and was well tolerated.		
Investigational Drugs and Formulations: 0.26 µg/kg Pitressin® (Parke-Davis) or saline 10 mL		
Administration: Intravenous injection		
Fed/Fasted: Overnight fasted, but not deprived of water		
Interfering Substances: Not indicated		
PK and PD Sampling Times: pre-dose, 10, 20, 30, 45 and 60 for the determination of growth hormone (GH), prolactin, TSH, FSH, LH and ACTH		

Analytical Method

After centrifugation the serum or plasma samples for each hormone were stored at -20 °C until analysis. All samples from each subject were analyzed in duplicate in the same assay run.

AVP

Plasma AVP was measured after extraction. The antiserum cross-reacted <0.1% with oxytocin. The assay sensitivity was 1 pmol/L and intra-and inter-assay coefficients of variation were 8.1 and 18 %, respectively.

Analyte		AVP
Method		RIA
Matrix		Plasma
Range, ng/mL		Not indicated
Quality Control	%CV	Not indicated
	%RE	Not indicated

Reference ID: 3313815

ACTH

Plasma ACT was measured by an immuno-radiometric assay using (^{125}I) of intact ACTH (Euro-Diagnostics Scientific Library, Apeldoorn, The Netherlands) The intra-assay CV ranged between 2.3 and 4.5% and the inter-assay CV ranged between 3.1% and 5.2%.

GH,TSH, FSH, LH

The serum levels of GH, prolactin and TSH were analyzed by fluoro-immuno assays (Delfia, LKB, Finland). For serum GH the intra-assay CV was 5%. For serum prolactin the intra-assay was ranging between 2 .1 and 2.6 % and the inter-assay CV was 6%. The reference range for prolactin is was 2-12 µg/L. For serum TSH the intra- and inter-assay CV were 5% and 6.9%, respectively, and the reference range 0.3-3.8 mIU/L. The serum levels for LH and FSH were measured by an immunoradiometric assay (Farmos Diagnostics, Turku, Finland) The reference range for LH was 1.9-9.4 IU/L and for FSH 1.3-9.0 IU/L. For FSH the intra-assay and inter-assay CV were 3.0 % and 4.2%, respectively, and for the LH assay they were <5.5%.

Target PK Parameters: Not indicated

PK Data Analysis: No PK data analysis was performed

Target PD Parameters: Change in AUC0-1h for ACTH, prolactin GH, TSH, FSH, and LH , blood pressure and pulse rate. The respective AUCs for ACTH, prolactin, FSH and LH were read off from the below Figure 2 by the Reviewer.

Statistical Methods/Sample Size/Power: The Wilcoxon Matched Pairs Signed Rank test was used to compare hormone responses to AVP and saline injections. The selected sample size is not based on power considerations.

Results

Study Population:

Randomized	9
Treated	9
Completed	9
Discontinued: withdrawal from study at request of subject	0
Pharmacokinetic population	9
Safety population	9
Age (Range)], years	23 (20-24)
Weight [Mean (SD)], kg	Not indicated
Male/Female	9/0
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated

PK of AVP

The mean (SEM) plasma concentrations of AVP as a function of time are shown in a linear plot below:

Reference ID: 3313815

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Fig 1. Plasma levels of AVP, pmol/L, after intravenous injection of AVP, 0.26 g/kg body weight (x—x) or saline ●--●. The bars indicate SEM

Fitting the mean data to a one compartmental model without subtracting the levels of endogenous AVP yielded V_D= 205 L and apparent t1/2 = 20 min. Considering that the first blood sample was taken 10 min after injection, the V_D obtained by extrapolation is overestimated.

PD

Linear plots of the mean (SEM) plasma- and serum concentration time curves as well as the corresponding AUCs for ACTH, prolactin, TSH and LH after injection of AVP and saline are shown below:

Reference ID: 3313815

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Injection of AVP increases the AUC of ACTH and prolactin significantly, whereas TSH and LH show only a trend for an increase. The AUC0-60 min after AVP for ACTH, prolactin, FSH and LH were 2.25, 1.35, 1.13 and 1.15 greater than after isosaline. The AUC for GH and FSH were not impacted by the administration of AVP. The onset of the effect of AVP on the secretion of ACTH, prolactin, TSH and LH occurred within 10 min and the hormones attained their prior steady-state again about 60 min after injection.
The levels of ACTH, prolactin, FSH and LH tended to decrease after saline in accordance with the diurnal rhythm with elevations of the levels earlier in the morning followed by a decay later in the morning. Stress can increase the levels of the pituitary hormones. However, the fact that GH was not elevated and the hormone levels tended to fall after saline suggests that the subjects were not stressed by the investigations. Blood pressure and heart rate after injection of AVP did not change relative baseline.

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
Within a few seconds of the injection of AVP, the subjects showed facial pallor and some experienced slight abdominal discomfort for 1-2 min that faded within few minutes.

Conclusion

PK

- The estimated apparent t1/2 after injection of AVP is 20 min

PD

- Injection of 9.83 U AVP increases the AUC0-60 of ACTH and prolactin 2.25 and 1.35 fold, respectively, whereas the AUC0-60 for TSH, LH, FSH and GH are not impacted relevantly.

Reference ID: 3313815

• Onset of the effect of AVP on ACTH, prolactin, FSH and LH is within 10 min after injection. About 60 min following AVP injection these hormones attain their steady-state again. • Study caused stress appears not to be a confounding factor for the increase in the hormone levels after injection of AVP • Blood pressure and heart rate after injection of AVP do not change relative to baseline Limitations of the study include that: • The information on the RIA for AVP provided is minimal • Blood samples for measuring AVP and the hormones should have been collected earlier than 10 min after AVP injection to better define the initial phase of AVP disposition and time of onset of the effect and magnitude of the peak activity on the hormones.
Comments
• None

2.5

Report #	**Study Period:** Not indicated	**EDR Link**
Title	Effects of Incremental Infusions of Arginine Vasopressin on Adrenocorticotropin and Cortisol Secretion in Man. Hensen J, Hader O, Baehr VE, Oelkers W. J Endocrinol Metab 1988; 66: 668-671	
Study Design: Single group study, with 5 randomized sequential treatments with 4 doses of AVP and normal saline**.** The administrations of AVP were separated by 7 days. The subjects were admitted to the Clinic at 1500. They assumed the supine position. Their prior food and fluid intake was unrestricted.		
Rationale: AVP regulates ACTH release under certain conditions, and exogenous AVP is used clinically to stimulate ACTH secretion. It is not known at what plasma concentration level of AVP the stimulation of ACTH ensues.		
Objectives: Primary: Determine level of AVP required to stimulate ACTH.		
Screening: Not indicated		
Periods: 5		
Treatments: 30 min intravenous infusions of 0.9% NaCL, AVP 10 ng/min, 30 ng/min, 100 ng/min and 300 ng/min.		
Sequence: The sequence of the infusions with 0.9% NaCL or AVP was randomized		
Dose Selection: Infusions of 10 to 300 ng AVP/min are considered safe		
Investigational Drugs and Formulations: AVP Ferring (Kiel) dissolved in 150 mmol/L saline or saline only		
Administration: Intravenous administration of 0.9% NaCL, 10 ng/min, 30 ng/min, 100 ng/min and 300 ng/min.		
Fed/Fasted: Not indicated		
Interfering Substances: No restrictions were applied		
PK Sampling Times: at 10, 20, 30, 40, 50, 60, and 70 min after infusion start. The		

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infusion lasted 60 min.

PD Sampling Times: Blood pressure (BP) and pulse rate were measured every 5 min

Analytical Method

PK

Analyte		AVP
Method		RIA
Matrix		Plasma
Range, ng/mL		Not indicated
Quality Control	%CV	Not indicated
	%RE	Not indicated

The tubes containing the blood samples were put into crushed ice and centrifuged immediately at 4° C, and the plasma was stored for no longer than 6 weeks at -70° C until assay. The AVP concentrations were measured by RIA. The antibody was provided by Dr. JJ Morgan (Glasgow) after extraction of the plasma using SepPak C18 cartridges. As AVP binds to platelets, 1 mL plasma just above the red cell layer after centrifugation was not removed for AVP measurement. The intra-and inter-assay variability was 4.9 and 8.8%, respectively.

The plasma concentrations of ACTH and cortisol were measured by RIA.

All analyses were performed in duplicate. All samples of a particular individual were analyzed at the same time.

PD

Osmotic pressure was measured by freezing point depression. Systolic and diastolic blood pressure (BP) was measured by an automated sphygmomanometer.

Target PK Parameters: CL

PK Data Analysis: The Reviewer calculated clearance of AVP from CL=ko/Css, where ko is the infusion rate and Css is the mean steady-state concentration of AVP at 40, 50 and 60 min.

Target PD Parameters: Plasma concentration time profiles of ACTH and cortisol. Osmolarity in plasma and urine, BP and pulse rate

Statistical Method/ Sample Size/Power: Duncan's multiple range test was used. The sample size selected was not based on statistical considerations.

Results

Study Population:

Randomized	6
Treated	6
Completed	5
Discontinued	1
Pharmacokinetic population	5
Safety population	6
Age [Range], years	24-28
Weight [Mean (SD)], kg	Not indicated
Male/Female	6/0
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated

Reference ID: 3313815

PK

The mean plasma concentrations of AVP, ACTH and cortisol vs. time are shown in the below figure:

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Reference ID: 3313815

The below table lists the mean plasma concentrations of AVP read off from the above figure at different times up to 60 min during infusion rates of 30 and 100 ng/min:

Mean (SEM) Plasma Concentrations of AVP Measured Pre-dose and during the 60 Minute Infusions of 30 and 100 ng/min[a]

Time min	AVP Infusion Rate ng/min	
	100	300[b]
0	0.4	0.4
10	34.9	191
20	51.4	255
30	51.0	249
40	58.1	291
50	51.0	270
60	65.5	277

[a] the corresponding plasma concentrations during the infusions with rates of 10 and 30 ng/min could not be read off reliably from the above figure [b] n=5

Mean Steady-State Concentrations and Body Weight Normalized Clearance of AVP

Infusion Rate ng/min	Css pg/mL	CL* mL/kg/min
100	57.8	24.7
300	276.6	15.5

* Assuming body weight of 70 kg

PK of AVP

The read off dose normalized plasma concentrations during the infusion with the rate of 300 ng/min were systematically higher than those during the infusion at a rate of 100 ng/min. The respective CL values were 24.7 and 15.5 mL/kg/min.

PD

ACTH and Cortisol Levels

A shown in the above figure the ACTH levels attain rapidly a maximum value 20 min into the infusions with AVP and dissipate rapidly thereafter. In contrast, the increase in the levels of cortisol is more protracted. The rise of the plasma concentrations of cortisol starts only 30 min after start of the infusions with AVP. Apparent peak concentrations of cortisol are attained at 60 min or later suggesting a counter-clockwise hysteresis of the effect of ACTH on cortisol triggered by AVP. The below table lists for ACTH and cortisol the ratios of the levels during the infusions with AVP to the levels during the control experiment:

Reference ID: 3313815

AVP Infusion Rate	Ratio of Peak Levels during Infusions with AVP and Placebo	
ng/min	ACTH	Cortisol
10	1.5	1.4
30	1.7	1.4
100	2.1	1.8
300	4.2	3.0

The values of the respective peak ratios for ACTH and cortisol in the presence and absence of AVP indicate that AVP infused at a rate of 300 ng/min increases ACTH 4.2 fold and cortisol 3.0 fold relative to placebo.

Safety: No side effects were reported during the infusions of AVP in the healthy subjects up to a rate of 100 ng/min. However, all subjects exhibited a slight facial pallor when given 300 ng/min AVP. Four of the 6 subjects complained about slight abdominal discomfort and flatulence. One subject reported nausea necessitating discontinuation of the infusion. The nausea dissipated fast after infusion stop. The results of this subject were not included in the data analysis.

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusions

- The dose normalized concentrations of AVP during the 100 ng/min infusion rate were greater than during the 300 ng/min infusion rate. The respective CL values were 24.7 and 15.5 mL/min at the two dose levels.
- The CL values for AVP were systematically greater than those found by others I healthy subjects (1-3). A possible explanation for this discrepancy is that Hensen et al. measured AVP in platelet poor plasma. AVP is reportedly bound to the platelets (4). The fact that Hensen et al. reported the lowest endogenous AVP concentrations among the selected publications supports this notion. The apparent dose dependent pharmacokinetics of AVP suggested by the data by Hensen et al. may indicate a saturable binding of AVP to the thrombocytes at higher concentrations.
- In the presence of AVP doses ranging between x-y U/min the peak concentrations of AVP are increased between 1.5 and 4.2 fold relative to placebo and the apparent peak concentrations of cortisol are increased between 1.4 and 3.0 fold. The AVP induced elevation of ACTH is transient. The ACTH effect on cortisol is delayed, but appears to last longer.
- Limitation of the study: The levels of cortisol should have been followed for a longer time period to be sure that the 60 min value reflects the true peak effect of AVP on cortisol.

Comments

- None

References

1. Moses AM, Steciak E. Urinary and metabolic clearances of arginine vasopressin in normal subjects. Am J Physiol186;251:R365-R370.
2. Moses AM, Jones C, Yucha CB, Effects of sodium intake, furosemide, and infusion of atrial natriuretic peptide on the Urinary and Metabolic Clearances of arginine vasopressin in normal subjects. J Endocrinol Metab1990;70:222-229
3. Davison JM, Sheills EA, Barron WM, Robison AG, Lindheimer MD. Changes in metabolic clearance of vasopressin and in plasma vasopressinase throughout human

Reference ID: 3313815

pregnancy. J Clin Invest 1989;83:1313-1318
4. Bichet DG, Arthua M-F, Barjon JN, Lonergan M, Kortas C. Human platelet fraction of arginine-vasopressin. J Clin Invest1987;79:881-887

2.6

Report #	**Study Period:** Not indicated	**EDR Link**
Title	Effects of Vsopressin in the Circulation and its Baroreflex Control in Healthy Men. Aylward PE, Floras JS, Leimbach WN, Abboud FM. Circulation 1986;73,1145-1154	

Study Design: Two parallel group design. The resting circulatory variables systolic, diastolic and mean arterial blood pressure (SBP, DBP, MAP), pulse pressure (PP), central venous pressure (CVP), heart rate (HR), forearm flow (FBF) and forearm vascular resistance (FVR) were assessed in four sequential periods of approximately 30 min each in 11 healthy male subjects. Period 1 was a control period with administration of the vehicle. During Periods 2 and 3 the subjects received infusions of AVP at 0.4 and 4.0 ng/kg/min, respectively. Period 4 was another control period with infusion of the vehicle beginning 30 min after cessation of the higher dose of AVP. Four (4) of the 11 subjects received only one of the AVP infusions (0.4 or 4.0 ng/kg/min. In addition the impact of reflex stimulation by lower body negative pressure (LNBP) inducing reflex vasoconstriction (application of negative pressure) or vasodilation (sudden cessation of negative pressure) was studied in 11 subjects. During LBNP the lower half body was enclosed up to the iliac crest in a sealed chamber and LBNP is applied for 2 min during each period. Seven (7) subjects participated in the neck suction and pressure experiments that were to impact HR. There were 3 study periods lasting approximately 30 min each. In Period 1 vehicle saline was infused, in Periods 2 and AVP was infused at rates of 0.4 and 4.0 ng/kg/min.

Rationale: Published articles indicate that AVP's potency to raise blood pressure in subjects with idiopathic orthostatic hypotension is greatly increased when compared to healthy subjects. In healthy subjects ganglionic blockade is needed to detect the pressor effect of AVP. Thus AVP may facilitate the inhibitory influence of baroreflexes on circulation.

Objectives: Primary: to assess the influence of AVP on the circulation and on baroreceptor control of vascular resistance and heart rate in healthy male subjects

Endpoints: SBP, DBP, MAP, PP, CVP, FBF, FVR

Inclusion Criteria: Not indicated

Exclusion Criteria: Not indicated

Screening: Not indicated	**Washout:** Not applicable
Periods	Not applicable

Treatments: AVP infusions at rates of 0.4 and 4 ng/kg/min

Sequence	Not applicable

Dose Selection: Doses up to 500 mU AVP given as intravenous bolus have been tolerated in healthy subjects

Investigational Drugs and Formulations: AVP Pitressin ® (Parke-Davis Inc.) diluted in 5 % dextrose

Reference ID: 3313815

Administration: Constant intravenous infusion through central venous catheter

Fed/Fasted: Not indicated

Interfering Substances: Not indicated

PK Sampling Times: Baseline blood samples for the determination of AVP were collected immediately after obtaining informed consent, but before placing the catheters, and after insertion of the catheters, but before any intervention and after completion of the reflex stimulation protocol. AVP values at each dose level represent the mean of those in two samples, one taken 10 min after initiation of the AVP infusions just before reflex stimulation and the other one taken on completion of the reflex stimulation after approximately 30 min of infusion. The recovery levels of AVP were collected 30 min after cessation of the AVP infusions.

PD Sampling Times: The publication does not state when the hemodynamic variables were measured. One must assume that the PD measurements were made 30 min into the infusions.

Analytical Method

Analyte		AVP
Method		RIA
Matrix		Plasma
Range, ng/mL		Not indicated
Quality Control	%CV	Not indicated
	%RE	Not indicated

The cross-reactivities for related peptides were LVP 27%, arginine vasotocine 5% and ocytocin <0.1%. The lowest level of sensitivity was 0.24 μU/tube. The inter- and intra-assay coefficients of variation are 9.8% and 6.5%, respectively. The reference provided does not indicate the precautionary measures taken to ascertain stability of AVP in the samples collected until assaying (1).

PD Methods: Blood pressure was measured via a pressure transducer via a radial artery cannula. Central venous pressure was measured via a catheter placed into an intra-thoracic vein. Forearm blood flow (FBF) was measured by venous occlusion plethysmography. For each intervention FBF was the mean of 4 - 8 measurements at 15 sec intervals over 2 min. Forearm vascular resistance (FVR) was calculated by dividing MAP by FBF

Target PK Parameters: Plasma concentrations of AVP

PK Data Analysis: Not applicable

Target PD Parameters: FBF, FVR, MAP, SBP, DBP, HR

Statistical Method/Sample Size/Power: The statistical analysis of the data used the paired t-test. Because multiple comparisons were performed the Bonferroni correction was used. The selected sample size is not based on power considerations.

Results

Reference ID: 3313815

Study Population:

Treated Completed Discontinued Pharmacodynamic population Safety population	18 18 0 18 18
Age [Range], years	18-35
Weight [Mean (SD)], kg	Not indicated
Male/Female	11/0
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated

PK

The below table summarizes the mean (SEM) plasma concentrations represented the average of values measured 10 and 30 min into the infusions in 18 young healthy males:

Study Periods	Mean AVP Concentrations after 10 and 30 min into Infusions
Infusion of	pg/ml
Vehicle	5.5 (0.4)
0.4 ng/kg/min AVP	24 (4)
4.0 ng/kg/min AVP	290 (41)
Vehicle	20 (4)[a]

[a] measured 30 min after infusion with 4.0 ng/kg/min was stopped

Of note averaging the 10 and 30 min concentrations is only justified if AVP attained a PK steady state at ≥ 10 min into the infusions. The authors do not provide evidence supporting this notion.

PD

<u>Effect of AVP on the Resting Hemodynamic Variables</u>

The effect of vehicle and AVP infusions on the resting hemodynamic variables are listed in the below table for the 18 subjects tested:

Reference ID: 3313815

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During AVP infusion at a rate of 0.4 ng/kg/min CVP increased significantly (+35 %) and HR (-3%) decreased significantly. AVP at a rate of 4 ng/kg/min increased CVP (+ 58%) and HR (+8%) and reduced SBP (-6%) and PP (-15%) significantly. Also, FBF increased at the higher rate significantly (+34%)

The effect of the AVP infusions on the hemodynamic variables before and during the application and release of LBNP (-40 mmHg) are shown in the below table:

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Reference ID: 3313815

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AVP did not exert any significant effect on the reflex responses on forearm vasoconstriction or vasodilation induced by application or release of LBNP - 40 mmHg, respectively, either at a rate of 0.4 or 4.0 ng/kg/min in 11 young, healthy subjects. However, AVP at a rate of 4.0 ng/kg/min after release of LBNP decreased FVR significantly indicating vasodilation.

The reflex response of the heart rate was not altered during application of neck pressure or suction in the 7 young healthy subjects.

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

- AVP at a rate of 0.4 ng/kg/min increases CVP significantly and decrease HR slightly. AVP at a rate of 4 ng/kg/min increases HR, CVP, FBF and reduces SBP, PP and FVR significantly, indicating vasodilation. Reflex vasodilation is also enhanced

Limitations of the study:

- AVP was dissolved in 5% dextrose for the purpose of intravenous administration. The sponsor claims that AVP and 5% dextrose are incompatible. It can be calculated that < 10% of AVP degrades in the presence of 5% dextrose during the 30 min infusions.
- The study periods were 30 min long and blood samples for the determination of AVP were taken 10 and 30 min after initiation of the infusions and averaged on the tacit assumption that AVP attains a steady-state ≥ 10 min after initiation of the infusions. No evidence supports this assumption. Therefore, no parameters could be derived from the measured plasma concentrations.
- The times for the measurements of the PD variables are not indicated

Comments

- None

Reference

1. Matsuguchi H, Schmid PG, Van Orden D, Mark AL. Does Vasopressin contribute to Salt-Induced Hypertension in the Dahl Strain? Hypertension 1981;3:174-181

Reference ID: 3313815

2.7

Report #	**Study Period:** Not indicated	**EDR Link**
Title	Vasopressin-Mediated Forearm Vasodilation in Normal Humans. Hirsch AT, Dzau VJ, Majzoub JA, Creager MA. J Clin Invest 1989;84:418-426.	
Study Design: Three experiments were performed using a parallel group design: 1. The dose-response profile of forearm blood flow (FBF) after intra-arterial administration of AVP was studied in 7 subjects. FBF was measured in the experimental and control arm. Heparinized normal saline was infused during all baseline periods. After establishing a stable baseline, AVP was infused at constant rates of 0.01, 0.1, 1.0 and 10 ng/kg/min in sequential 20 min study periods. Two additional subjects served as time and vehicle controls by undergoing the same protocol with intra-arterial infusion of the vehicle chlorobutanol. 2. The systemic hemodynamics, forearm and digital blood flow responses to intra-arterial AVP infusion alone and following pre-treatment with the vasopressin V_1 receptor antagonist d$(CH_2)_5$Tyr(Me)AVP were studied in 10 additional subjects. Systolic and diastolic blood pressure (SBP, DBP), heart rate (HR), FBF and digital blood flow (DBF) responses were determined during 5 sequential 20 min study periods: At baseline, after intra-arterial infusion of AVP at 1.0 ng/kg/min, second baseline, after intravenous administration of 0.5 mg of the V_1 AVP antagonist alone, and after re-challenge with AVP 1.0 ng/kg/min during V_1 AVP receptor blockade. Of note the FBF and DBF measurements were only conducted in 7 subjects. 3. The dose-response profile of the systemic hemodynamics, FBF and DBF after intra-arterial administration of the V_2 agonist 1-desamino [8-D-arginine] vasopressin with AVP at rates of 0.01, 0.1 and 1.0 ng/kg/min in sequential 20 min study periods were studied in 5 subjects. Two of the subjects had previously participated either in the first or second study.		
Rationale: AVP exhibits renal hydrosmotic effects via V_2 receptors and arterial vasoconstriction mediated by V_1 receptors. Potent vasoconstrictor effects of AVP have been demonstrated in vitro and during high dose infusions in animals (1,2). However, in humans only modest increases in blood pressure or systemic vascular resistance have been observed.. In addition, there is evidence that AVP may also display vasodilatory effects by not well defined mechanisms. AVP increases release of vasodilating prostaglandins and endothelium–dependent relaxant factor and decreases renin secretion.		
Objectives: a) To determine the direct vascular effect of AVP in the human forearm independent of reflex effects by measuring the forearm blood flow (FBF) b) To clarify the role of specific receptors mediating these vascular effects via either co-administration of a specific V_1 vasopressin receptor antagonist or by infusing dDAVP, a vasopressin V_2 receptor antagonist c) To relate local changes in vasodilator prostaglandin levels to changes in FBF during AVP infusion d) To determine whether AVP's vascular effects are regionally selective by measuring blood flow to the finger as well as to the forearm		
Endpoints: FBF, DBF, BP, HR		
Inclusion Criteria: Young, healthy subjects of both sexes		
Exclusion Criteria: Subjects with hepatic, renal or cardiac disease		

Reference ID: 3313815

Screening: Medical history, physical examination, laboratory testing to exclude cardiac renal and hepatic diseases	**Washout:** Not applicable
Periods	Not applicable
Treatments: 1. AVP alone 2. AVP after pre-treatment with V_1 antagonist $d(CH_2)_5Tyr(Me)AVP$ 3. AVP after pre-treatment with V_2 agonist desmopressin	
Sequence	Parallel group study (except for 2 subjects who participated in 2 of the 3 studies)
Dose Selection: Significantly larger infusion rates than 10 ng/kg/min have been administered intravenously	
Investigational Drugs and Formulations: AVP Pitressin® (Parke-Davis, Morris-Plains, NJ), $d(CH_2)_5Tyr(Me)AVP$ (CIBA-Geigy AG, Basel, Switzerland), dDAVP Desmopressin® (USV Laboratories, Inc. Tarrytown, NY), chlorobutanol (Sigma Chemicals Co., St. Louis, MO)	
Administration: Intra-arterial via brachial artery	
Fed/Fasted: Overnight fasted	
Interfering Substances: Alcohol, caffeine and cigarette smoking within 12 h of study start was prohibited	
PK Sampling Times: Study Protocols 1 and 2**:** Venous blood samples for the determination of AVP and vasodilator prostaglandin concentration were measured 15 min after initiation of the infusion in the experimental and control arms.	
PD Sampling Times: Study Protocols: SBP, DBP, HR, FBF and DBF responses were measured 20 min after initiation of each infusion. FBF and DFB were the means of 5 determinations taken at intervals of 10-15 sec.	

Analytical Method
PK

Analyte		AVP
Method		RIA
Matrix		Plasma
Range, ng/mL		Not indicated
Quality Control	%CV	Not indicated
	%RE	Not indicated

The blood samples collected were immediately placed on ice, centrifuged at 2 °C and the plasma stored at -70 °C until assaying. AVP was measured after extraction in triplicate using an RIA. The assay had a sensitivity of 0.2 pg/tube, a cross-reactivity of < 0.005% with oxytocin, however displayed a 100 % cross reactivity with $d(CH_2)_5Tyr(Me)AVP$. The intra-assay coefficient of variation was 9%.

PGE_2 and the PGI_2 metabolite 6-keto-$PGF_{1\alpha}$ were determined in unextracted plasma from effluent venous blood by RIA. With this RIA PGE_2, 6-keto-$PGF_1\alpha$, thromboxane B_2 and PGE_2 and $PGF_{1\alpha}$-M exhibit a cross-reactivity <1%. These prostaglandin assays have a sensitivity of 10 pg/mL and an intra-assay coefficient of variation < 10%

PD

Reference ID: 3313815

Occlusion plethysmography was used to measure FBF using strain gauges. Forearm and digital venous occlusion pressure was 40 mm Hg. SBP and DBP were measured via intra-arterial catheter connected to a transducer.
Target PK Parameters: Plasma concentrations of AVP in venous blood of experimental and control arm
PK Data Analysis: Not applicable
Target PD Parameters: SBP, DBP, HR, FBF ,DBF,
Statistical Method/Sample Size/Power: The data from each study period were compared by analysis of variance for repeated measures for parametric data, followed by Neuman-Keuls posthoc testing for statistical significance. Friedman's analysis of variance for repeated measures was used for non-parametric data. The selected sample size was not based on power considerations.
Results

Study Population:

Study 1	
Randomized	9
Treated	7
Completed	7
Discontinued	0
Controls	2
Pharmacokinetic population	7
Study 2	
Randomized	10
Treated	10
Completed	10
Discontinued	0
Pharmacokinetic population	10
Study 3	
Randomized	5
Treated	3
Completed	3
Discontinued	0
Controls	2
Pharmacokinetic population	3
Safety population	22
Age [Mean (SD)], years	26 (5)
Weight [Mean (SD)], kg	Not indicated
Male/Female	13/9
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated

Study 1. AVP Dose-Response

PD

BP and HR

Reference ID: 3313815

The effect on SBP and DBP when AVP was administered at constant infusion rates of 0, 0.01, 0.1, 1.0 and 10.0 ng/kg/min shown in the below table was not significantly different indicating no impact of vasopressin on BP:

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The HR increased slightly (+10%), but significantly during infusion of AVP at the top rate of 10 ng/kg/min.

FBF

The dose-response for FBF in the experimental and control arms is shown in below figure and table::

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Mean (SEM) Forearm Blood Flow

Infusion Rate of AVP	Experimental Arm	Contra-lateral Arm
ng/kg/min	mL/100 mL/min	
Baseline	3.5 (0.4)	3.4 (0.4)
0.1	4.5 (1.0)	Numerical value not indicated[a]
1.0	5.4 (0.9)*	Numerical value not indicated[a]
10.0	5.5 (1.3)*	6.5 (1.5)*

[a] not statistically significantly different from baseline * statistically significant different from baseline

The data show a statistically significant increase during the intra-arterial AVP infusions with the 1.0 and 10.0 ng/kg/min rates of 54 and 57%, respectively, in the experimental arm. The effect reached a plateau during the infusion with 1.0 ng/kg/min as the infusion of AVP at the rate of 10 ng/kg/min did not show an increment in FBF. No effect on FBF

Reference ID: 3313815

was seen with the control arm except during the infusion with the 10.0 ng/kg/min rate which triggered a statistically significant effect similar to that in the experimental arm. In contrast, after infusion of the vehicle no change in FBF or SBP was seen as shown in the below table:

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The PGE_2 and 6-keto-PGF1α levels

PGE_2 and 6-keto-PGF1α levels at baseline or after infusion of 1.0 ng/kg/min AVP did not change relevantly during Study Protocol 1.

PK

The venous plasma levels of AVP in the experimental (E) and control (C) arms measured 15 min into the infusions are shown in the below table:

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The mean concentrations of endogenous AVP during vehicle administration in the experimental and contra-lateral arms are about 3 ng/mL. During the infusions with AVP the mean plasma concentrations in the experimental and control arms increase with dose. The concentrations in the experimental and control arm during the infusions with only the 2 top doses were approximately dose proportional.

Study 2. Effect of AVP after V_1 Receptor Blockade

Reference ID: 3313815

PD

BP and HR

The duration of action of the V_1 receptor blocker is >2 h. The impact of intra-arterial administration of the vehicle, AVP at a rate of 1.0 ng/kg/min alone, and the V_1 receptor antagonist alone and co-administered with AVP on SBP, DBP and HR is shown in the below table:

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The intra-arterial infusion of AVP alone at a rate of 1.0 ng/kg/min, as expected, showed BP and HR effects comparable to those seen during the infusion with vehicle. Administration of the V_1 antagonist alone did not impact the hemodynamics. In contrast, infusion of the same dose of AVP after pretreatment with the V_1 antagonist $d(CH_2)_5$Tyr(Me)AVP resulted in a statistically significant reduction of DBP (- 9%) and an increase in HR (+ 26 %).

FBF

The impact of AVP infused at a rate of 1.0 ng/kg/min on FBF in the presence and absence of the V_1 receptor antagonist is shown in the below figure:

Reference ID: 3313815

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The increase in FBF in the experimental arm during intra-arterial infusion of AVP alone at a rate of 1.0 ng/kg/min was statistically significant (4.5 mL/100 mL/min). However, following intravenous pretreatment with the V_1 antagonist $d(CH_2)_5$Tyr(Me)AVP the effect of AVP infused at 1.0 ng/kg/min was 1.67 fold greater (7.5 mL/100 mL/min) than in the absence of the V_1 antagonist suggesting paradoxically that the V1 antagonist potentiates the effect of the V1 agonist on FBF. FBF was unchanged in the controls. Of note the infusion rate of 1.0 ng/kg/min as previously determined yielded the maximum vasodilatory effect.

DBF

The impact of AVP infused at 1.0 ng/kg/min in the presence and absence of the V_1-receptor antagonist $d(CH_2)_5$Tyr(Me)AVP is shown in the below figure:

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In the absence of the V_1 antagonist DBF decreased statistically significantly during the intra-arterial AVP infusion in the experimental arm. Basal DBF was re-established 20 min after stopping the infusion of AVP. Administration of the V_1 antagonist alone did not affect DBF. In the presence of the V_1 antagonist the vasoconstrictor effect of AVP was abolished.

Reference ID: 3313815

The PGE_2 and 6-keto-$PGF_{1\alpha}$ levels

PGE_2 and 6-keto-$PGF_{1\alpha}$ levels at baseline or after infusion of 1.0 ng/kg/min AVP did not change relevantly during Study Protocols 2.

PK

The venous plasma concentrations of AVP in the presence and absence of AVP and the V_1 antagonist are shown in the below table:

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The baseline levels of endogenous AVP were between 4 and 5 pg/mL and slightly higher than during study Protocol 1. The plasma concentration during infusion of 1.0 ng/kg/min AVP in the experimental arm was only 45% of that seen in Study Protocol 1 with the same infusion rate, whereas the concentrations of the contra-lateral arm in Protocols 1 and 2 were comparable. Of note, despite the difference in the plasma concentrations the effect of AVP on FBF was comparable in Study Protocols 1 and 2.

Study 3. FBF Dose-Response Relationship for the V_2 Agonist dDAVP

BP and HR
The impact of the dDAVP infusions on BP and HR are shown in the below table:

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The infusion of dDAVP did not impact DBP or HR at any dose level. However, SBP was slightly, but significantly reduced (-5%) after infusion of the top dose of 1.0 ng/kg/min dDAVP.

Reference ID: 3313815

FBF and DBF

Intra-arterial infusions of the V_2 agonist dDAVP at a rate of 0.1 ng/kg/min increased FBF in the experimental arm significantly. Increasing the rate of infusion to 1.0 ng/kg/min augmented FBF even more as shown in the below Figure:

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The impact of the intra-arterially administered V_2 agonist dDAVP on DBF appeared to be insignificant as shown in the below figure:

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Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

- Intra-arterial infusions of AVP in the range between 0.01-10 ng/kg/min do not change SBP or DBP significantly. HR is also unchanged with the 0.01 and 0.1 ng/kg/min infusion rates. A small (+10%) but significant increase in HR is observed at the top rate of 10 ng/kg/min.
- Intra-arterial infusions of AVP increase FBF in the infused arm in a dose dependent manner with a maximum increase of 54-57% at infusion rates of 1.0 and 10 ng/kg/min. A comparable increase of FBF is observed in the control arm only after the 10.0 ng/kg/min dose.

Reference ID: 3313815

- Intravenous pre-treatment with the V_1 antagonist $d(CH_2)_5Tyr(Me)AVP$ potentiates the vasodilatory effect of intra-arterial administered AVP at a rate of 1.0 ng/kg/min and FBF is increased by +167%.
- AVP intra-arterially infused at a rate of 1.0 ng/kg/min decreased DBF significantly. In the presence of the V_1 antagonist $d(CH_2)_5Tyr(Me)AVP$ the vasoconstrictor effect of AVP was abolished.
- Intra-arterial infusions of the V_2 agonist dDAVP causes a dose dependent increase in FBF, but does not impact DBF. Thus, the vasodilatory effect seen with AVP may be due to a V_2 receptor mediated action of AVP. However, the effect of AVP is not uniform throughout a vascular region as shown by the increase in FBF, but reduction of DBF.
- PGE_2 and 6-keto-PGF1α levels are not impacted by AVP.

Limitations of the study:

- The dose of the V1 antagonist administered intravenously is not indicated
- The PD variables are measured 20 min into the infusions. Blood samples for measuring AVP are collected 15 min into the infusions. The authors compare the results obtained in the experimental and control arms. However, whereas steady-state for PK and PD may be attained fast in the experimental arm, it takes 4 ● t1/2 until AVP or dDAVP attain a steady-state for PK in the control arm. The publication does not provide evidence supporting attainment of a steady-state for PD or PK of the study drugs.

Comments

- The abstract of the publications should be corrected to state that AVP at a rate of 10 ng/kg/min increased FBF in the control arm.

References

1. Monos E, Cox R, Peterson LH. Direct effect of physiologic doses of arginine vasopressin on the arterial wall in vivo. Am J Physiol 3:H167-H172
2. Cowley AW, Switzer SJ, Guinn MM. Evidence and quantification of the vasopressin arterial pressure control system in the dog. Circ Res 1980;46:58-67

2.8

Report #	**Study Period:** Not indicated	**EDR Link**
Title	Biphasic Forearm Vascular Responses to Intra-Arterial Arginine Vasopressin. Suzuki S, Takeshite A, Imaizumi T, Hirooka Y, Yoshida M, Ando S, Nakamura M. J Clin Invest 1989; 84:427- 434	

Study Design: Three (3) group parallel design**.** In 6 subjects the dose-response relationship for the forearm blood flow was studied using doses of 0.05, 0.1. 0.2, 0.5 and 1.0 ng/kg/min infused for 2 min intra-arterially. Forearm blood flow (FBF) was continuously measured in the ipsilateral arm using venous occlusion plethysmography. In 7 subjects attempts were made to explore the mechanism responsible for the vasodilatory effect observed at higher AVP levels. To exclude the possibility that systemic neural effects are involved FBF was measured in the ipsi-lateral and contra-lateral arm in 5 subjects. AVP was infused for 2 min

Reference ID: 3313815

intra-arterially at rates of 1.20 and 2.0 ng/kg/min. To examine whether the vasodilatory effect of AVP is due to stimulation of prostaglandin synthesis. The impact of AVP was examined before and after treatment of the subjects with oral indomethacin (75 mg/day for 3 days) in 5 subjects. In 6 subjects the impact of intra-arterial calcium chloride (0.09 meq/min) was investigated because plasma ionized calcium may attenuate the vasodilatory effect of AVP. Calcium chloride infusion was infused for 10 min followed by a treatment with simultaneous administration of AVP and calcium chloride at two doses. The effect of increased plasma ionized calcium on forearm vasodilation by sodium niroprusside and isoproterenol was also investigated In 3 subjects sodium nitroprusside (1.7, 3.3, 6.7 ng/kg/min) and in 4 subjects isoproterenol (0.08, 0.17, 0.33 ng/kg/min) was administered intra-arterially. Subsequently, the measurements of FBF were repeated during simultaneous administration of calcium chloride and sodium nitroprusside in 3 subjects. Some subjects participated in more than one of the substudies.
Rationale: Conflicting vasoconstricting and vasodilating effects have been reported in the literature after intra-arterially infused AVP. Previous studies have indicated that AVP may stimulate endogenous prostaglandin synthesis in blood vessels and kidney.
Objectives: Primary: To assess the direct effect of AVP after intra-arterial administration and to explore the underlying mechanism of action Secondary: To assess the impact of AVP on prostaglandin levels after pre-treatment with indomethacin.
Endpoints: MAP (diastolic blood pressure + 1/3 pulse pressure), HR, FBF, FVR
Inclusion Criteria: Not indicated
Exclusion Criteria: Not indicated
Screening: Not indicated / **Washout:** Not applicable
Periods / Not applicable
Treatments: Intra-arterial saline, AVP, calcium chloride, sodium nitroprusside, oral indomethacin
Sequence / Not applicable
Dose Selection: The respective doses were for: AVP: 0.05, 0.1, 0.2, 0.5, 1.0 ng/kg/min, sodium nitroprusside: 1.7, 3.3 and 6.7 ng/kg/min, isoproterenol 0.08, 0.17, 0.33 ng/kg/min, calcium chloride: 0.09meq/min and indomethacin: 75 mg/day for 3 days (considered to be pharmacologically effective and safe)
Investigational Drugs and Formulations: AVP Pitressin ® (Parke-Davis, Morris-Plains, NJ), sodium nitroprusside (Wakou Junyaku Kougyou, Osaka, Japan) , isoproterenol (Proterenol ®, Nikken Kagaku, Tokyo, Japan)
Administration: AVP, sodium nitroprusside, isoproterenol, and calcium chloride intra-arterially infused for 2 min, indomethacin po
Fed/Fasted: Not indicated
Interfering Substances: Not indicated
PK Sampling Times: Not indicated
PD Sampling Times: Not indicated
Analytical Method PK Analyte: AVP

Reference ID: 3313815

Method		RIA
Matrix		Plasma
Range, ng/mL		Not indicated
Quality Control	%CV	Not indicated
	%RE	Not indicated

AVP was measured in duplicate after extraction of plasma with Sep-Pak C18 cartridge (1). The respective cross-reactivity of the antiserum was 0.04% with LVP, 0.19% with dDAVP and < 0.01% with oxytocin, and vasotocin. The recovery ranged between 79- 99% at AVP concentrations of 0.46-7.38 pmol/L plasma. The results were corrected for recovery. The intra- and inter-assay coefficient of variation was 7.8% and 7.4%, respectively, for AVP concentrations of 1.06 and 1.38 pmol/L. The reference does not indicate how stability of AVP was ascertained in the collected blood samples until assaying.

Target PK Parameters: Plasma concentrations of AVP

PK Data Analysis: Not applicable

Target PD Parameters: MAP, HR, FBF, FVR, plasma concentrations of cGMP, cAMP and ionized calcium. FVR was obtained by dividing MAP by FBF

Statistical Method: /Sample Size/Power: The results on the response parameters to intra-arterial administration of AVP, sodium nitroprusside or isoproterenol used a one-way analysis of variance (ANOVA). The Newman-Keuls multiple comparison test was used to determine the statistical significance when comparing the values for the controls with those at each dose of the drugs. Two-way ANOVA was used to compare forearm vascular response to AVP before and after indomethacin and to compare the response to the drug in the presence and absence of co-administered other drugs. A paired t-test was used to compare plasma concentrations of AVP, cAMP and cGMP and ionized calcium between saline and drug infusions. The selected sample size is not based on power considerations.

Results

Study Population:

Treated Completed Discontinued Pharmacodynamic population Safety population	20 20 0 20 20
Age [Mean (SE)], years	21(0.4)
Weight [Mean (SE)], kg	61(2)
Male/Female	20/0
Race (Caucasian/Black/Hispanic/ Asian/Other)	Asian

PD

Relationship of between AVP Dose and Hemodynamic Variables

The below table summarizes the results obtained in 6 subjects:

Reference ID: 3313815

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The AVP infusions at rates ranging between 0.05-1.0 ng/kg/min do not impact MAP or HR. However, the ipsilateral FVR is increased 55 and 28 %, respectively at rates of 0.05 ng/kg/min and FBF reduced 35% at a rate of 0.05 ng/kg/min AVP. At the higher rates of 0.2,0.5 and 1.0 ng/kg/min AVP reduces FVR by 22, 34 and 47% respectively, and increases FBF by 37, 58 and 94%, respectively.
The biphasic nature of the exposure-response relationship and the percent changes in FBF are shown in the below figure:

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Forearm Vascular Response to Infusions of AVP, before and after Pretreatment with Indomethacin and during Simultaneous Administration of Calcium Chloride

The results are listed in the below table:

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AVP infused at rates of 1.0 and 2.0 ng/kg/min reduces FRV by 72 and 169%, respectively, and increases FBF by 40 and 64%, respectively, in the ipsilateral arm as expected. The varying results on FBF and FVR obtained in the 2 experiments with 1.0 ng/kg/min AVP suggest significant intra-subject variability. The contra-lateral arm shows no change in FBF or FVR.
After pretreatment with indomethacin AVP dose dependently reduces FVR and increases FBF. Pre-treatment with indomethacin has no impact on the response to AVP.
Co-infusion of AVP and calcium chloride abolishes the vasodilatory effect of AVP.
Plasma levels of cAMP and cGMP are not significantly impacted by AVP.

Sodium nitroprusside, like AVP, looses its vasodilatory effect (ipsilateral forearm) in the presence of calcium chloride as demonstrated by the results listed in below table:

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Reference ID: 3313815

The cGMP levels were not impacted by the infusion of sodium nitroprusside.

The equivalent vasodilatory effect the β_1, β_2 agonist isoproterenol exhibited at rates of 0.06, 0.17 and 0.33 ng/kg/min in the presence and absence of calcium chloride suggests no impact of calcium chloride on the vasodilatory activity of isoproterenol as shown below:

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The cAMP levels were not impacted by the infusion of calcium chloride.

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

- Intra-arterial infusions of AVP at rates ranging between 0.1-1.0 ng/kg/min do not impact MAP or HR.
- AVP is a forearm vasoconstrictor at low infusion rates of 0.05-0.1 ng/kg/min and a forearm vasodilator at rates of 0.2-1.0 ng/kg/min. The vasodilation is dose dependent with significant intra-subject variability.
- A 3 day pre-treatment with indomethacin (75mg/day) has no impact on forearm vasodilation by AVP
- $CaCL_2$ infusions abolish forearm vasodilation by AVP
- The forearm vasodilation induced by intra-arterial AVP is not mediated by prostaglandins

Comments

- None

Reference

1.Watabe T, Tanaka K, Kumgae M, Itoh S, Kogure M, Hasegawa M, Horiuchi T, Morio K, Takeda F, Ubukata E, Miyabe S, Shimizu N. Role of endogenous a\rginine vasopressin in potentiating corticotropin-releasing hormone-stimulated corticotropin secretion in man. J Clin Endocrinol Metab 1988; 66:1132-1137

Reference ID: 3313815

3. DDI in Adults

3.1

Report #	**Study Period**: Not indicted	**EDR Link:**
Title	Oestrogen Effects on Urine Concentrating Response in Young Women. Stachenfeld NS, Taylor HS, Leone CA, Keefe DL. J Physiol 2003;552.3: 869-880	
Study Design: To suppress reproductive function for the duration of the study 5 healthy young women were administered daily leuprolide acetate for 5 weeks. For 4 days at the end of the fifth week the women received estrogen. Experimental protocols were performed at the end of the fourth week (GnRHa alone administration) and at the end of the fifth week (GnRHa + estrogen administration). This design permitted within subjects comparisons of estrogen effects on renal response to AVP. The subjects were to be non-smokers and have regular 26-32 day menstrual cycles. The subjects self-administered an oral dose of 300 mg lithium carbonate at 2200 h before each experiment, which provided a near constant plasma level of lithium by the next morning. For each experiment the subjects arrived at the laboratory at 0700 h after having eaten a light (~300 kcal) breakfast, having drunk 10 mL/kg of water. After a 60 min control period in semi-recumbent position a pre-dose measurement of BP was taken and a urine sample collected. Then the subjects received an intravenous bolus injection of 10 mg/kg PAH followed by a zero order infusion of 10.25 mg /kg PAH. Subsequently, the serial AVP infusion treatments at rates of 10, 35, 100, 150 and 200 μU/kg/min were started.		
Rationale: There is evidence suggesting that estrogen may lower renal tubular sensitivity to AVP. However, during the menstrual cycle elevations of estrogen is always accompanied by elevations of progesterone, so that the individual effects of the hormones are difficult to assess in young women.		
Objectives: Primary: To determine whether estrogen attenuates the urine concentrating effect of AVP young women received treatments with the gonadotropin releasing hormone antagonist (GnRHa) leuprolide acetate alone and with GnRHa + estrogen.		
Screening: Not indicated	**Washout:** Not applicable	
Periods	2	
Treatments: Intravenous infusions of AVP at ascending infusion rates of 0, 10, 15, 35, 100, 150 and 200 μU/kg/min for 60 min in the presence of leuprolide acetate alone and leuprolide acetate + 17β-estradiol (0.1mg/day), lithium carbonate		
Sequence	Crossover with fixed sequence; first treatment leuprolide alone then treatment with leuprolide + 17β-estradiol	
Dose Selection: The AVP infusion rates were chosen so that the plasma concentration of AVP would not exceed about15 pg/mL. At his level AVP is not expected to exhibit effects on BP. Leuprolide 0.5 mg/day by subcutaneous self administration, 17β-estradiol (0.2mg/day) via 2 transdermal patches and lithium carbonate 300 mg taken orally are expected to have their expected effects.		
Investigational Drugs and Formulations: Lupran ® (TAP Pharmaceuticals, Deerfield, IL), Transdermal patch Vivelle (CIBA Pharmaceuticals, Summit, NJ), synthetic AVP (Pitressin®, Parke-Davis, Morris Plains, NJ)		
Administration: Leuprolide subcutaneously, 17β-estradiol transdermally, AVP		

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intravenously, lithium carbonate orally

Fed/Fasted: Fed (light breakfast ~ 300 kcal)

Interfering Substances: Subjects on oral contraceptives stopped intake of the contraceptives and initiated the leuprolide treatment in the third week. Subjects were to refrain from alcohol and caffeinated beverages and were to be non-smokers.

PK Sampling Times: Blood samples were collected every 30 min and urine samples every 60 min for the determination of renal clearance and osmoregulatory functions. The subjects drank 100 mL tap water immediately following each urine sample.

PD Sampling Times: Blood pressure and heart rate were recorded every 15 min throughout the infusions. Blood samples and urine samples were collected every 60 min for the determination of osmoregulatory functions. Hourly blood samples were collected for the determination for albumin, serum sodium and potassium, lithium and PRA, estrogen, progesterone. Renal prostaglandin E_2 was measured in al urine samples.

Analytical Method

PK

Analyte		AVP
Method		RIA
Matrix		Plasma
Range, ng/mL		Not indicated
Quality Control	%CV	Not indicated
	%RE	Not indicated

The blood samples for the determination of AVP were centrifuged at 4˚C and the plasma frozen immediately at -70 ˚C until assaying. The plasma was extracted using octadecylsilane catridges (SepPakC_{18}). The extraction efficiency was 87%. Extraction recovery of AVP was determined using plasma spiked with a known concentration of AVP (Pensinsula Laboratories, Belmont CA). The recovery sample was extracted and analyzed along with the subjects' samples. The antiserum is prepared against a lysine vasopressin-thyroglobin conjugate. The sensitivity is 0.6 pg/mL. Intra- and inter-assay coefficients of variation for the mid range standards (10.3 pg/mL) were 15 and 16%, respectively.

PD

Osmolality in plasma and urine were determined by a freezing point depression method. Plasma concentrations of PRA, estrogen PGE2 in urine were measured by RIA.

Target PK Parameters: Css, CL

PK Data Analysis: Clearance was calculated from CL=ko/Css

Target PD Parameters: Osmolality in plasma and urine, SBP, DBP, RPF

PD Data Analysis: The AVP concentrations before and after log transformation plotted vs. urine osmolality were fitted by a sigmoidal function and EC_{50} and log EC_{50} determined.

Statistical Method:

Sample Size/Power: An analysis of variance (ANOVA) for repeated measures was used Sample size was calculated based on the findings from an earlier study showing that 8 subjects are sufficient to attain 80% power to determine a statistically significant change in uine osmolality.

Results

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Study Population:

Randomized Treated Completed Discontinued Pharmacokinetic/dynamic population Safety population	5 5 5 0 5 5
Age [Mean (SD)], years	23 (1)
Weight [Mean (SD)], kg	70(3.9)
Male/Female	0/5
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated

PK

The below table lists the mean steady-state plasma concentrations and clearances after AVP infusions at ascending rates with the two treatments:

Mean Steady-State Plasma Concentrations and Clearances of AVP after Infusions with 10, 35, 100, 150 and 200 μU/kg/min AVP in the Presence of GnRHA + Estrogen and in the Presence of GnRHa alone

Infusion Rate	Css[a]		CL[b]		Ratio CL[c]
μU/kg/min	pg/mL		mL/kg/min		
	Leu	E2+ Leu[d]	Leu	E2+Leu[d]	
0	1.4 (0.1)	1.2 (0.2)	-	-	
10	4.1 (0.9)	2.6 (0.6)	0.77	1.1	1.43
35	5.2 (0.8)	4.0 (0.7)[e]	2.2	3.2[f]	1.45
100	7.6 (1.2)	5.8 (0.9)[e]	5.1	8.6[f]	1.69
150	10.6 (1.1)	7.9 (1.0)[e]	7.5	9.0[f]	1.20
200	11.1 (0.5)	11.2 (0.5)[e]	7.0	8.1[f]	1.16

[a] Plasma concentrations of AVP 60 min after infusion b read off from Figure 4
[c] Ratio of CL with estradiol+ leuprilide treatment to Leuprolide alone treatment
[d] estradiol + leuprolide [e] significantly smaller in presence of estradiol + leuprolide than in presence of leuprolide alone [f] significantly greater in presence of estradiol + leuprolide than in presence of leuprolide alone

The CL of AVP in the presence of estradiol + leuprolide is 1.39 fold greater than in the absnece of estradiol suggesting a smaller exposure to AVP with the combination treatment.

PD

The values obtained for selected target parameters after administering AVP at ascending infusions rates are shown below:

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No treatment difference was observed in plasma osmolality, and free water clearance. None of the other parameters including diastolic, systolic BP, heart rate or renal blood flow changed relative to baseline or vary among the treatments. Also, the renal sensitivity to AVP, i.e. the renal concentrating response measured as urine osmolality was comparable with both treatments. Both treatments reduced urine flow and increased urine osmolality significantly relative to baseline, but this is probably due to the fact that the subjects were more hydrated at baseline than during the remainder of the experimental periods.

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

- Estrogen treatment does not affect the renal concentrating response to graded AVP infusions.
- The CL of AVP with the two lower infusion rates appears to be smaller than with

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the 3 upper infusion rates with both treatments. • The clearances of AVP administered at rates of 30, 100, 150 or 200 μU/kg.min are between 16-49% greater in the presence of estradiol + GnRHa than in the presence of GnHRa alone suggesting that the exposure to AVP is smaller with the combination treatment. • Urine flow decreases and urine osmolality increases significantly with both treatments relative to baseline • The infusions of AVP have no effect on blood pressure, heart rate or renal blood flow
Comments
• None

3.2

Report #	**Study Period**: Not indicated	**EDR Link**
Title	Plasma Levels of Antidiuretic Hormone in Patients Receiving Prolonged Lithium Therapy. Padfield PL, Park SJ, Morton JJ, Braidwood AE. Brit J Psychiat 1977;130:144-147	
Study Design: Parallel group study with a group of 18 patients with manic-depressive disorders on long term therapy with lithium carbonate and 34 controls, 16 patients with mild psoriasis and 18 healthy subjects, were studied under similar conditions.		
Rationale: The authors had previously reported on a patient who developed gross polyuria while taking lithium carbonate while AVP levels were found to be high or at the upper end of normal. They postulated that plasma AVP might rise in response to polyuria, but because of insensitivity to the hormone would fail to compensate for the fluid loss. To test this hypothesis, patients attending a lithium clinic in intervals of about 2 months who did not have obvious diabetes insipidus were studied.		
Objectives: Primary: To measure AVP in patients treated with lithium carbonate and compare the levels with those observed in		
Endpoints: Plasma concentrations of AVP		
Inclusion Criteria: Patients with manic-depressive disorders treated chronically with lithium carbonate		
Exclusion Criteria: Patients on chronic lithium carbonate therapy with obvious diabetes insipidus		
Screening: Not indicated	**Washout:** Not applicable	
Periods	Not applicable	
Treatment: Lithium carbonate		
Sequence	NA	
Dose Selection: The mean dose of lithium the patients were receiving was 1.2 (0.1) g/day (mean SEM)		
Investigational Drugs and Formulations: Lithium Carbonate Priadel ®		
Administration: Oral		
Fed/Fasted: Overnight fasted		
Interfering Substances: Smokers were asked to refrain from smoking the evening before		

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the study day. In addition to lithium carbonate 3 patients were receiving chlorpromazine (50-100 mg tid), 2 amitryptiline (25 mg tid), and 1 depot phenothiazine (1 patient was receiving both chlorpromazine and amitryptiline)

PK and PD Sampling Times: Blood samples were collected between 9 and 10 AM on the study day for the determination of plasma AVP, serum lithium, osmolality in plasma, urea and serum potassium. A urine sample was taken at the same time for the determination of urine osmolality.

Analytical Methods

AVP

Analyte		AVP
Method		RIA
Matrix		Plasma
Range, ng/mL		Not indicated
Quality Control	%CV	Not indicated
	%RE	Not indicated

After collection the blood samples were immediately centrifuged at 5˚ C and the plasma removed and extracted or stored for maximally 2 weeks at -20 ˚ C until assaying. AVP was extracted using a modified florisil technique. Standard curves with known amounts of AVP 2-250 pg AVP in 200 µL Trisbuffer were set up. The recovery of AVP in spiked plasma was about 60%. The respective coefficients of variation for within batch and between batch reproducibility were 13 and 9 %, respectively. The lowest AVP concentration measurable in plasma was 2.0 pmol (=2.2 pg/mL). AVP in plasma is stable when deep frozen for 2 weeks at -20 ˚C.

Lithium

The concentrations were measured by atomic absorption spectro-photometry.

Target PK Parameters: Endogenous AVP concentrations in plasma

PK Data Analysis: The Reviewer read the mean (SEM) endogenous AVP off Figure 1.

Target PD Parameters: Plasma osmolality. All patients were asked the below questions by the same observer (SP) to determine possible polydipsia and polyuria:

1. **Have you noticed any alteration in your drinking habits?**

If so:

2. **Are you more or less thirsty than you used to be?**
3. **Do you pass urine less frequently, or more frequently than you used to?**
4. **Do you get up at night to pass urine? If so, how often?**
5. **How long have these changes been present?**

Sixteen (16) in-patients (8 females), suffering from affective disorders, were asked identical questions for comparison by another observer (AEB)

Statistical Methods: Not indicated.

Sample Size/Power: The selected sample size was not based on power considerations.

Results

Reference ID: 3313815

Study Population:

Manic-depressive patients		18
Treated		18
Completed		18
Discontinued		0
Pharmacokinetic population		18
Safety population		18
Controls		34
Treated		34
Completed		34
Discontinued		0
Pharmacokinetic population		34
Safety population		34
Age [Mean (SD)], years	Manic-depressive patients	Not indicated
	Controls	Not indicated
Weight [Mean (SD)], kg	Manic-depressive patients	Not indicated
	Controls	Not indicated
Male/Female	Manic-depressive patients	13/5
	Controls	Not indicated
Race (Caucasian/Black/Hispanic/ Asian/Other)	Manic-depressive patients	Not indicated
	Controls	Not indicated

The manic-depressive patients had been treated with lithium carbonate for on average 29 months (6-84) months. The mean (SEM) serum lithium concentrations was 0.8(0.1) mmol/L. In all patients blood urea was < 6.8 mmol/L and serum potassium >3.0 mmol/L. No patient had glycosuria.

PK

The lithium concentrations of the patients ranged from 0.3-1.5 mmol/L.

The individual plasma concentrations measured in the patients and the controls are shown in the below figure:

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The mean (SEM) values for the plasma concentrations of AVP and plasma and urine osmolality are provided in the below table:

Subjects	AVP	Plasma Osmolality	Urine Osmolaity
	pg/mL	mmol/kg	mmol/kg
Manic-depressive Patients	7.2 (0.5)*	296(1.0)	621(39)
Controls	5.9 (0.3)	295(0.8)	693(38)

* statistically significantly different

The plasma concentrations of AVP were statistically significantly greater in the patients on lithium carbonate than in the controls not taking lithium carbonate, but there was wide scatter of the data. Plasma osmolality was not different among the groups, whereas urine osmolality tended to be lower than in the controls.

There was no relationship between AVP concentrations and the severity of symptoms, the duration of lithium theapy or the the serum levels of lithium.

PD

Polyuria and Polydipsia

Thirteen (13) of the 18 patients complained of increased thirst. Of these 11 had noticed an increase in frequency of micturition. Nine (9) patients complained of nocturia. In 5 this was accompanied by subjective complaints of polyuria and polydipsia and in 3 of polyuria alone. In no case did the symptoms antedate the introduction of lithium carbonate, but the time interval from the start of lithium and the onset of the symptoms varied widely from an almost immediate onset to a delay of 6 years. None of the in-patients complained of a change in drinking habits, urinary frequency or nocturia.

Safety

Reference ID: 3313815

▪ Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
Conclusion
• Although the RIA assay for AVP used in the publication based on today's standards cannot be considered validated, the results are acceptable. If the assay is biased the bias in the values goes in the same direction in both groups so that a real difference between the populations if present, is detected. • Long term intake of lithium carbonate increases AVP levels and tends to decrease urine osmolality in the patients whereas plasma osmolality is similar in both groups. The increased incidence of polyuria and polydipsia in the patients on chronic lithium carbonate therapy suggests that lithium interferes with water and possibly electrolyte excretion, and the observed increase in AVP may be compensatory. • A review article published recently indicates that lithium counteracts the intracellular signaling pathway of AVP. In addition to polyuria and polydipsia , renal tubular acidosis and finally chronic renal failure as well as renal diabetes insipidus are associated with long term lithium carbonate therapy (1).
Comments
• None
Reference 1. Trepiccione F, Moenster-Christenssen B. Lithium-induced nephrogenic diabetes insipidus: new clinical and experimental findings. J Nephrol 2010;23:S43- S48.

3.3

Report #	**Study Period**	**EDR Link**
Title	Inappropriate Vasopressin Secretion in Severe Alcohol Withdrawal. Trabert W, Caspari D, Bernhard P, Biro G. Acta Psychiatrica Scandinavica 1992;85 376-379	
Study Design: A group of 41 male alcoholics suffering from alcohol withdrawal were investigated for 10 consecutive days.		
Rationale: Rising alcohol concentrations inhibit the secretion of AVP resulting in an augmented diuresis with loss of free water. A status of hyperhydration due to impaired water excretion and increased AVP was found in acute withdrawal states (1). Based on this finding an inappropriate secretion of AVP (SIADH) resulting in water intoxication and cerebral edema was postulated (2). Some postmortem studies have shown increased brain water content that may be responsible for the known demyelinisation diseases (central pontine myelinosis or Korsakoff syndrome (3). However, previous studies did not measure the osmotic pressure along with the concentrations of AVP. Elevated values of AVP should only be interpreted when information on the osmotic pressure is available.		
Objectives: Primary: To determine the relationship between AVP levels and osmotic pressure during the withdrawal phase of alcoholics		
Endpoints: Serum and urine levels of endogenous AVP and osmotic pressure in serum and urine		
Inclusion Criteria: Alcoholics admitted to the hospital because of alcohol withdrawal syndrome		

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Exclusion Criteria: Schizophrenia, affective psychosis, polytoxicomania, cardiac, renal or liver failure, hypotension (< 120 mmHg) or prior intake of anticonvulsants		
Screening: Not indicated		**Washout:** Not applicable
Periods	Not applicable	
Treatment: Not applicable		
Sequence	Not applicable	
Dose Selection: Not applicable		
Investigational Drugs and Formulations: Not applicable		
Administration: Not applicable		
Fed/Fasted: Not indicated		
Interfering Substances: Smoking within 30 min of blood sample collection for the determination of AVP was prohibited		
PK Sampling Times: Days 1, 2, 3, 5 and 10: determination of endogenous AVP levels in plasma and urine after 30 min rest in supine position		
PD Sampling Times: Withdrawal state was assessed with the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A) scale on admission, and Days 2, 3, 5, and 10 (between 0700 an 0800. Serum sodium, potassium urea, glucose, albumin, creatinine, serum and urine osmolality on Days 1, 2, 3, 5 and 10		

Analytical Method

Analyte		AVP
Method		RIA
Matrix		Plasma
Range, ng/mL		Not indicated
Quality Control	%CV	Not indicated
	%RE	Not indicated

The publication did not contain any additional information on the RIA method used.

Target PK Parameters: Plasma levels of endogenous AVP

PK Data Analysis: Not applicable

Target PD Parameters:

Statistical Method/Sample Size/Power: Non-parametric tests, an analysis of variance (ANOVA) and discriminant analysis were performed. The selected sample size was not based on power considerations.

Results

Study Population:

Age [Mean, Range)], years	43 (26-64)
Weight [Mean (SD)], kg	Not indicated
Male/Female	41/0
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated

The duration of the alcohol dependence was 10 (2-40) y. The mean daily consumption of alcohol was 200 (80-840) g for the last 4 weeks prior to admission. Eight of the 41

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withdrawing alcoholics developed full delirium tremens (DT) within the first 24 h

PK, PD

The mean (SEM) endogenous serum concentration of AVP, serum osmolality and the CIWA-A scores during the withdrawal phase are shown in the below table:

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The plasma concentrations of AVP fell statistically significantly from 3.08(0.61) pg/mL on admission to 1.65 and 1.71(0.22) pg/mL on Days 5 and 10, respectively. Serum osmolality did not show a time dependency suggesting an increased secretion of AVP in alcoholics during withdrawal. A post-hoc stratification of the subjects who experienced a DT and those who did not showed significantly higher AVP concentrations for a given osmolality in the DT group than in the DT free group.
Discriminant analysis with serum osmolality and serum ADH as independent variables showed 100 % correct classification to the DT Group and 87% to the Non-DT group.

References
1. Eisenhofer G, Johnson RH. Effects of ethanol ingestion on plasma vasopressin and water balance in humans Am J Physiol 1982;242:R522-R527
2. Elmsley RA, Potgieter, Taljaard JJF, Coetzee D, Joubert G, Gledhill RF. Impaired water excretion and elevated plasma vasopressin in patients with alcohol withdrawal symptoms. Q J Med:244:671-678
3. Lambie DG. Alcoholic brain damage and neurologic symptoms of alcohol withdrawal manifestations of overhydration. Med Hypoth 1985;16:377-388

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

- The highest mean serum level of AVP 3.08 pg/mL in alcoholics with withdrawal is found on admission.
- By Day 5 and 10 the AVP levels are reduced significantly to 1.65 and 1.71 pg/mL, respectively, whereas osmolality in serum do not exhibit a time dependent pattern suggesting an increased AVP secretion in alcoholics during withdrawal that is independent of osmotic pressure.

Comments

- The units of the serum concentrations of AVP in Table 1 should read pg/mL not pg/nL.

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• The AVP concentrations and the osmolality in urine were not reported.

3.4

Report #	Study Period	EDR Link
Title	Interaction of Vasopressin Infusion, Corticosteroid Treatment, and Mortality of Septic Shock. Russell, JA, Walley KR, Gordon AC, Cooper DJ, Hebert O, Singer J, Holmes CL, Mehta S, Granton T, Storms MM, Cook DJ, Presneill JJ, Ayers D for the Vasopressin and Septic Shock Trial (VASST) Investigators. Crit Care Med 2009, 37, 2009	
Study Design: Randomized double-blind, active control. Patients with catecholamine refractory septic shock were randomized to receive either vasopressin (0.01-0.03 U/min) or norepinephrine (5-15 µg /min). Open-label vasopressors were titrated to mean arterial blood pressure (MAP) >65-75 mm Hg. This is a post hoc sub-study of the multicenter, randomized, blinded and controlled study of vasopressin vs NE reviewed by the Reviewer in another review. The administration of corticosteroids was not protocolized. The administration of corticosteroids was determined by clinicians caring for the patients at each center. Type dose and route of administration of all corticosteroids were recorded in all patients over the 28 day primary observation period. "Use of corticosteroids" was defined as the administration of corticosteroids for at least 1 day during the 28 day observation period. Patients were accordingly classified as "corticosteroid treatment" or " no- corticosteroid treatment".		
Rationale: Vasopressin and corticosteroids are often added to support cardiovascular dysfunction in patients with septic shock that is non-responsive to fluid resuscitation and norepinephrine (NE) infusion. It is unknown whether vasopressin treatment interacts with corticosteroid treatment.		
Objectives: Primary: To investigate a possible interaction between corticosteroids and vasopressin		
Screening: see review of VASST study	Washout: Not applicable	
Periods	Not applicable	
Treatment: see review of VASST study		
Sequence	Not applicable	
Dose Selection: See review VASST study		
Investigational Drugs and Formulations: see review of VASST		
Administration: Vasopressin and NE by intravenous infusion, intravenous infusion of open-label vasopressors		
Fed/Fasted: Not stated		
Interfering Substances: Not stated		
PK Sampling Times: Blood was collected for the measurement of vasopressin levels in a convenience sample in 6 of the participating institutions (n=107) 6 and 24 h after initiation of vasopressin infusion.		
PD Sampling Times: see review of VASST study		
Analytical Method: See review of VASST study		
Target PK Parameters: Plasma concentrations of vasopressin 6 and 24 h after initiation of vasopressin infusion		
PK Data Analysis: None		
Target PD Parameters: See review of VASST trial		
Statistical Method/Sample Size/Power: see review of VASST trial		
Results		

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Study Population:

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[a]Statistical test (χ^2 or t test) comparing steroids plus norepinephrine vs. steroids plus vasopressin (Arginine vasopressin); [b]Statistical test (χ^2or t test) comparing no steroids plus norepinephrine vs. no steroids plus vasopressin (Arginine vasopressin).

The subgroup of patients on vasopressin receiving hydrocortisone had increased severity of illness compared to the sub-group of patients not receiving hydrocortisone. This is demonstrated by the baseline characteristics.

Of the 589 patients treated with corticosteroids, 296 received both vasopressin and corticosteroids and 293 received both norepinephrine and corticosteroids (of total 779 patients). Within this subgroup of patients who received corticosteroids, vasopressin and NE were matched except that the vasopressin treated patients were younger as shown in the above table

The hydrocortisone doses in the AVP and NE groups are shown in the below table:

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Of note some patients received dexamethasone, fludrocortisone and prednisone instead of hydrocortisone, but their dose were not different between the 2 groups.

PK

The plasma concentrations of AVP in the presence of NE and AVP are shown below:

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The plasma concentrations of AVP in the presence of corticosteroids are significantly greater than in the absence of corticosteroids; About 30% and 67% 6 h and 24 h after initiation of the treatments, respectively.
The authors conclude that patients who received vasopressin and corticosteroids had higher plasma concentrations than patients who di not receive corticosteroids.

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

- The observed increased exposure of vasopressin in the presence of corticosteroids should not be interpreted to indicate that corticosteroids interfere with the disposition of exogenous vasopressin.

- The study was not protocolized to test the hypothesis that corticosteroid treatment impacts the levels of exogenous vasopressin. The subgroup of patients receiving AVP and hydrocortisone were sicker than the subgroup of patients on AVP not receiving hydrocortisone. Thus, the clearance of AVP could have been smaller in the patients on corticosteroids, because they were sicker including more impaired organ function. The publication does not state whether the infusion rate of vasopressin was the same in the group receiving hydrocortisone and the group not receiving hydrocortisone.

Comments

None

Reference ID: 3313815

4. Special Adult Populations

4.1

Report #	**Study Period:** Not indicated	**EDR Link**
Title	Abnormal Pressor Response to Vasopressin in Patients with Cirrhosis: Evidence for Impaired Buffering Mechanism. Moreau R, Hadengue A, Soupison T, Mechin G, Assous M, Roche-Sicot J, Sicot C. Hepatology 1990;12: 7-12	
Study Design: Subjects with histology proven alcoholic cirrhosis with Child Pugh classification A-C and subjects histologically free of cirrhosis were enrolled.		
Rationale: The sustained vasoconstrictory effects of vasopressin which contribute to the ischemic side effects in patient with cirrhosis of the liver are known. The mechanism responsible for the sustained pharmacological effect of vasopressin in cirrhotics is not well understood.		
Objectives: Primary: To investigate whether mechanisms aimed at buffering the increase in arterial blood pressure by vasopressin are impaired in patients with cirrhosis and account for the sustained effect of AVP in patients with cirrhosis		
Endpoints: Mean arterial blood pressure (MAP), pulse pressure, heart rate (HR) , cardiac index (CI), stroke volume index (SVI), systemic vascular resistance (SVR), right atrial pressure, mean pulmonary artery pressure (MPAP), pulmonary wedged pressure, free hepatic venous pressure, hepatic venous pressure gradient, hepatic blood flow, plasma concentrations of sodium, potassium glucose and creatinine		
Inclusion Criteria: Histologically proven cirrhosis/ Absence of histologic cirrhosis		
Exclusion Criteria: Sepsis, baroreflex abnormality, heart failure, arterial hypertension, diabetes mellitus, coronary artery disease, alcohol withdrawal syndrome or polyneuritis		
Screening: Not indicated	**Washout:** Not applicable	
Periods	Not applicable	
Treatment: Intravenous infusion of 17 and 15 ng/kg/min lysine vasopressin (LVP) in cirrhotics and controls, respectively		
Sequence	Not applicable	
Dose Selection: 0.4 U/min LVP is the usual dose given to patients with bleeding esophageal varices		
Investigational Drugs and Formulations: LVP intravenous solution Source and manufacturer of the drug product are not indicated		
Administration: Intravenous		
Fed/Fasted: Overnight fasted		
Interfering Substances: No intake of alcohol for 10 days prior to study start, diuretics and vasoactive drugs were withdrawn at least 1 week prior to study start.		
PK Sampling Times: Protocol does not foresee measurements of vasopressin		
PD Sampling Times: Pre-dose 15 and 30 min after initiation of vasopressin infusion		

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Analytical Method Lysine vasopressin plasma concentrations were not measured
Target PK Parameters: Not applicable
PK Data Analysis: Not applicable
Target PD Parameters: MAP, HR, CI, SVI, SVR, right atrial pressure, MPAP, pulmonary wedged pressure, free hepatic venous pressure, hepatic venous pressure gradient, hepatic blood flow, plasma concentrations of sodium, potassium, glucose and creatinine. Hepatic flow was estimated by determining the clearance of indocyanine green. Hepatic flow was only determined in the controls. Only in the controls are splanchnic- and liver blood flow identical.
Statistical Method/ Sample Size/Power: One-way or two-way repeated measures ANOVA and paired and unpaired Student's t-tests were performed when appropriate. A Bonferroni correction for multiple comparisons was used. The sample size was not based on power considerations.

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Results

Study Population:

Randomized		12
Alcoholic cirrhotics with biopsy proven cirrhosis		6
Treated		6
Completed		6
Discontinued		0
Controls		6
Treated		6
Completed		6
Discontinued		0
Pharmacodyamic population		12
Safety population		12
Age [Mean (SD)], years	Cirrhotics	42(12)
	Controls	41 (3)
Weight [Mean (SD)], kg	Cirrhotics	67(13)
	Controls	61(12)
Male/Female	Cirrhotics	5/1
	Controls	4/2
Race (Caucasian/Black/Hispanic/Asian/Other)		Not indicated
Child-Pugh Classification of Cirrhotics:	A	2
	B	2
	C	2

The control group consisted of alcoholics with a histology negative for cirrhosis. In 4 of the control subjects the histology showed mild portal fibrosis and in 2 alcoholic steatosis.
The 6 patients with cirrhosis were functionally classified as Child-Pugh Class A, B or C.

PD

The mean(SD) plasma concentrations of sodium, potassium, glucose and creatinine shown in the below table for the two groups indicate comparable normal results:

	Sodium	Potassium	Glucose	Creatinine
	mmol/L	mmol/L	mmol/L	µmol/L
Cirrhotics	136(2)	3.9(0.2)	4.8(0.3)	77 (26)
Controls	136(3)	4.0(0.3)	4.8(0.6)	70(11)

As shown in the below tables in the patients with cirrhosis the pre-dose MAP was significantly lower than in the controls:

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The controls can be considered matched for age, body weight and sex.

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The infusion of vasopressin induced in both groups a biphasic response in MAP and HR: A peak increase in MAP occurred 5-9 min after infusion start and was followed immediately by a peak reduction in HR. In both groups, the peak values from of MAP and HR were significantly different from the baseline values. In the controls 30 min after infusion start MAP had returned to baseline, whereas HR, CI, systemic O_2 transport and consumption and hepatic blood flow were significantly lower than the pre-infusion values.
In contrast, in the cirrhotics 30 min after the start of the LVP infusion MAP, SVRI, right atrial and MPAP remained significantly higher than the baseline values. HR, CO, systemic O_2 transport and hepatic venous pressure gradient were significantly decreased relative to the pre-infusion values, as in the controls 30 min after injection of LVP.
The changes in MAP during LVP infusion are shown in the figure below for both groups:

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The change from baseline in MAP at peak time and after 30 min of infusion was significant. The authors explain the difference in the offset of the effect of LVP by an impaired circulatory reflex system in cirrhotics that is not able to buffer the effects of LVP

The pertinent results are summarized in the below table:

Change from Baseline in Mean Arterial Blood Pressure and Heart Rate in Cirrhotics and Controls During Infusion of 0.04 U/min AVP

Cirrhotics				**Controls**			
ΔMAP mm Hg		**ΔHR bpm**		**ΔMAP mm Hg**		**ΔHR bpm**	
Peak	30 min	Peak	30 min	Peak	30 min	Peak	30 min
26	13	-24	-16	20	0	-19	-11

The respective peak effects of AVP on MAP and HR when infused at a rate of 0.04 U/min is 1.3 fold greater than in the controls. Also the residual effects on MAP and HR 30 min after initiation of the infusion are greater in the cirrhotics of C-P Class A, B or C. The results suggest a small increase in peak effect and a more prolonged offset of the hemodynamic effects of AVP in cirrhotics. Increased exposure of AVP is more likely the cause for the observed difference than a change in receptors or signal pathway.

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

- The respective peak effects of AVP on MAP and HR when infused at a rate of 0.04 U/min is 1.3 fold greater than in the controls. Also the residual effects on MAP and HR 30 min after initiation of the infusion are greater in the cirrhotics of C-P Class A, B or C. The results suggest a small increase in peak effect and a more prolonged offset

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of the hemodynamic effects of AVP in cirrhotics. Increased exposure of AVP is more likely the cause for the observed difference than a change in receptors or signal pathway. • A limitation of the study is that the plasma concentrations of LVP were not measured so that the alternative explanation for the increased and prolonged effects of AVP in the cirrhotics, namely increased exposure could not be tested directly. • The pressor activity of the used LVP was not indicated
Comments
• None

4.2

Report #	**Study Period:**1979-1983	**EDR Link**
Title	Impiego della Vasopressina nel Trattimento delle Varici Esofagee Sanguinanti. Nostra Esperienza. Fornaro R, Ferraris E, Belcastro, E Parodi G. Min Med 1985;76: 1719-1726	
Study Design: Retrospective study in 12 cirrhotic patients with esophageal varices treated with intravenous or intra-arterial vasopressin. Vasopressin was administered intravenously when the hemorrhage persisted or restarted after a transient stop despite continued application of the initial therapeutic measure selected. The source of the bleeding was determined by arteriography. Vasopressin 0.2 U/min was administered over an initial period of 20 min using an infusion pump. Repeat arteriography after 20 min showed whether the hemorrhage had stopped. If the hemorrhage had stopped the infusion of vasopressin was maintained for 12 h at a reduced rate of 0.1 U/min, and then further reduced to 0.05 U/min for another 12 h and then stopped. If the hemorrhage continued the infusion rate was increased to 0.4 U/min for 20 min and then the arteriography repeated. In case the hemorrhage continued the patients underwent a surgical intervention or an arteriographic or endoscopic procedure. During the infusion of vasopressin serial ECGs were performed.		
Rationale: Nusbaum et al (1,2) reported that doses of vasopressin > 0.2U/min reduced mesenteric blood flow by ≥ 50% and subsequent diminution of portal vein pressure without affecting cardiac output. These authors (3) also suggested that intra-arterial administration of vasopressin may offer advantages over the intravenous route by increasing the concentration of vasopressin in the target tissue without increasing simultaneously the drug concentration in the mesenteric or coronary circulation.		
Objectives: Primary: Evaluate efficacy of vasopressin in terminating acute gastro-intestinal hemorrhages in patients with cirrhosis and incidence of adverse events		
Endpoints: Efficacy of treatment with vasopressin and incidence of adverse events		
Inclusion Criteria: Patients with acute digestive system hemorrhage due to ruptured esophageal varices diagnosed by esohagoduodenoscopy and/or selective visceral angiography		
Exclusion Criteria: Patients in who hemorrhage stopped spontaneously, after mechanical intervention (Sangstaken-Blakemore tube) or by pharmacological means (antacids, H_2-blockers administration of coagulation factors, coagulants, fresh plasma, transfusion of		

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blood or platelets). Also excluded were patients in whom an acute surgical intervention became necessary.		
Screening: Not indicated		**Washout:** Not applicable
Periods	Not applicable	
Treatment: Intravenous or intra- arterial infusions of vasopressin		
Sequence	Not applicable	
Dose Selection: 0.2-0.4 U/70 kg/min=0.0050U/kg/min		
Investigational Drugs and Formulations: Source and manufacturer of vasopressin was not indicated in publication		
Administration: intravenous or intra-arterial		
Fed/Fasted: Not indicated		
Interfering Substances: Not indicated		
PK Sampling Times: Blood samples for the determination of AVP were not collected		
Analytical Method: Not applicable		
Target PK Parameters: Not applicable		
PK Data Analysis: Not applicable		
Statistical Method/Sample Size/Power: Not indicated		
Results		
Study Population:		

Treated	Intravenous administration	12
Completed		12
Not completed		0
Pharmacokinetic population		Not applicable
Safety population		12
Treated	Intra-arterial administration	14
Completed		14
Not completed		0
Pharmacokinetic population		Not applicable
Safety population		14
Age [Mean,(Range)], years		56 (32-79)
Weight [Mean (SD)], kg		Not indicated
Male/Female		21/5
Race (Caucasian/Black/Unknown)		Not indicated

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The below table summarizes the clinical laboratory results of the study patients:

Laboratory Findings

	Group A	**Group B**
	Intravenous	Intra-arterial
Number of Patients	12	14
Unit of blood transfused	7.2	7.6
Bleeding varices	11	12
Varices and gastritis	1	2
Encephalopatia moderate	2	2
mild	4	5
absent	6	7
Ascites considerable	5	6
present	5	5
absent	5	3
Total bilirubin mg%	4.1	3.7
Serum albumin g%	2.78	2.72
Prothrombin time seconds > normal value	4.6	4
Partial thromboplastin time seconds > normal value	11	10
Number of platelets/mL	105 000	112 000
Number of patients with significant coagulation deficit	5	6

Efficacy

The below table lists the results on efficacy of vasopressin in stopping esophageal-intestinal hemorrhage and the survival of the patients:

Efficacy of Treatment with Vasopressin

	Group A	Group B
Complete stoppage of hemorrhage	7	7
Temporary stoppage of hemorrhage	2	3
Combined control by vasopressin and S-B[a] tube	1	2
No control of hemorrhage	2	2

[a]Sangstaken-Blackmore tube

Survival of Patients

	30 Day Survival	6 months Survival
Number of patients vasopressin effective	14	10
Number of patients vasopressin not effective	12	2

There was a trend for patients in whom vasopressin was effective to survive longer.

Safety

- Was there any death or serious adverse events? ☑ Yes ☐ No ☐ NA

The adverse events observed in the patients are listed in the below table:

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Adverse Events Observed and 30 Day Mortality

Complications related to catheter	1	3
Hypertension	1	0
Cardiac arrhythmias	2	4
30 day mortality	4	5

Six (6) of the 26 cirrhotic patients developed cardiac arrhythmias including bradycardia, Wenkebach phenomenon with second degree AV block. Treatment of the arrhythmias with lidocaine was necessary in 2 patients. In 5 patients the dose of vasopressin had to be reduced from 0.4-0.2 U/min to 0.2-0.1 U/min. Nine (9) patients had died by Day 30.

Conclusion

- No conclusion can be drawn on whether the apparently frequent incidence of arrhythmias observed in the cirrhotic patients (Child-Pugh Class A-C) is caused by a significantly increased exposure to AVP, a high hepatic extraction drug.

Limitations of the study include:

- Retrospective design, absence of a control group and appropriate statistical power
- The characteristics of the bradycardic arrhythmias observed are not well described.
- The cause of death of the non-surviving patients is not discussed by the authors

Of note other cases of bradycardic arrhytmias with subsequent development of Torsades de points in patients with alcoholic liver disease have been reported after administration of vasopressin and the structural analog desmopressin (4-8).

Comments

- None

References

1. Nusbaum M, Baum S, Sakiyalak P, Blakemore WS. Pharmacologic control of portal hypertension. Surg 1967; 62:299
2. Nusbaum, Baum S, Kuroda K et al. Control of portal hypertension by selective mesenteric arterial infusions. Surg 1968;97: 1005
3. Nusbaum M, Conn HO. Arterial vasopressin infusions: Science or séance? Gastroenterology 1975; 69:263
4. Mauro Vincent F, Bingle JF, Ginn SM, Jafri FM. Torsades de Pointess in a patient receiving intravenous vasopressin. Crit Care Med 1988;16:200-201
5. Fitz JD Vasopressin induction of ventricular ectopy. Arch Int Med 1982;142:644
6. Kelly KJ, Stang JM, Mekhjian HS. Vasopressin provocation of ventricular dysrrhytmia. Ann Int Med1980:92:205-206.
7. Eden E, Teirstein A, Wiener I. Ventricular arrhythmia induced by vasopressin: Torsade de Pointes related to vasopressin-induced bradycardia. Mountt Sinai J Med 1983; 50:49-51
8. Kupferschmidt H, Meir Ch, Sulzer M, Meier PJ, Buehler H. Der Klinisch-pharmacologische Fall (2) Bradycardia and ventricular tachyarrhythmia with Torsade de Pointes as side effect of vasopressin: Three case reports. Praxis (Bern 1994) 1996;85: 340-343

Reference ID: 3313815

4.3

Report #	**Study Period:** Not indicated	**EDR Link**
Title	Effect of Hemodialysis on Plasma ADH Levels, Plasma Renin Activity in Patients with End-Stage Renal Disease. Iitake K, Kimura T, Matsui K, Ota K, Shoji M, Inoue M, Yoshinaga K. Acta Endocrinologica 1985: 110: 207-213	

Study Design: Parallel design with 2 groups of subjects, a first group with 5 healthy subjects and a second group with 40 patients with ESRD. Endogenous AVP was determined in all subjects. The patients with ESRD were stratified into low and high renin subgroups based on their pre-dialysis level. The PK of exogenous AVP was determined in 5 healthy subjects and 4 patients with ESRD.

Rationale: There is controversy in the literature whether the elevated levels of AVP in ESRD are due to increased osmotic pressure in plasma or due to a failure of renal degradation or both.

Objectives: Primary: To clarify the regulatory mechanism of the endogenous AVP concentrations in patients with ESRD, the plasma concentrations of AVP, plasma renin activity (PRA) and plasma aldosterone were simultaneously determined before and after hemodialysis. The permeability of these hormones through the dialysis membrane was also investigated. In addition, the clearance of exogenous AVP was evaluated.

Endpoints: Plasma levels of endogenous AVP PK of exogenous AVP

Inclusion Criteria: Not indicated

Exclusion Criteria: Not indicated

Screening: Not indicated	**Washout:** Not applicable
Periods	Not applicable

Treatment: AVP bolus injection

Sequence	Not applicable

Dose Selection: 1.5 mU/kg AVP

Investigational Drugs and Formulations: AVP (Pitressin®, Sankyo-Parke Davis, Tokyo, J)

Administration: Intravenous bolus injection

Fed/Fasted: Not indicated

Interfering Substances: 10 of the 40 patients with ESRD were on clonidine, nifedipine, propranolol, hydralazine, methyldopa, or reserpine. Some patients took also $AL(OH)_3$, multivitamins or ferrous sulfate.

PK/PD Sampling Times: Blood samples for the determination of AVP, PRA and aldosterone, osmotic pressure, BUN ad creatinine were collected from the arterio-venous fistula just before and after hemodialysis.

Analytical Method
AVP

Analyte	AVP
Method	RIA
Matrix	Plasma

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Range, ng/mL		Not indicated
Quality Control	%CV	Not indicated
	%RE	Not indicated

The AVP in plasma was extracted with a resin column (1). The recovery of spiked plasma was about 72 %. The intra-and inter-assay coefficient of variation were 10.7% and 7.4%, respectively. The detection limit of the assay was 0.4 pg/tube. The respective cross-reactivity to deamino-D-arginine vasopressin, oxytocin, and lysine vasopressin was 0%, 0% and 0.5%, The PRA and aldosterone concentrations in plasma were measured by RIA.

Target PK Parameters: CL,V_D, t1/2

PK Data Analysis: A 2 compartment model was assumed based on the plasma concentration time curve established from concentrations measured at 3 time points, namely 10, 20 and 30 min after injection. It appears that the feathering technique was used to determine the two exponential phases. The respective V_D values were obtained by extrapolating of the two slopes and reading of the respective y-axis intercepts. The method used to calculate CL_1 and CL_2 from $CL_1=V_{D,1} \bullet (\ln 2/t1/2_1)$ and $CL_2=V_{D,2} \bullet \ln 2/t1/2_2$, respectively, is incorrect.

Target PD Parameters: Plasma osmolality and effective plasma osmolality. Effective plasma osmolality was obtained from EPosm=Posm – (BUN/2.8)

Statistical Method/Sample Size/Power: Paired t-tests were performed within a group and unpaired t-tests between groups. The selected sample size was not based on power considerations.

Results

Study Population:

Healthy Subjects			
Treated			5
Completed			5
Discontinued			0
Pharmacokinetic population			5
Safety population			5
Patients with ESRD			
Treated			40
Completed			4
Discontinued			0
Pharmacokinetic population			4
Safety population			4
Age [Range], years	Healthy Subjects		27-39
	Patients with ESRD		17-72
Weight [Mean (SD)], kg	Healthy Subjects		Not indicated
	Patients with ESRD	Pre-dialysis	47.8 (2.3)[a], 52.1(1.4)[b]
		Post-dialysis	46.6 (2.3)[a], 50.3(1.3)[b]
Male/Female	Healthy Subjects		4/1
	Patients with ESRD		20/20
Race (Caucasian/Black/Hispanic/Asian/Other)	Healthy Subjects		0/0/0/5/0
	Patients with ESRD		0/0/0/40/0

[a] Low renin subgroup, [b] high renin subgroup

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The mean (SEM) pre-dialysis renin levels in the low and high renin subgroups were 0.4 (0.1) and 2.8(0.4) ng/mL/h, respectively.
The clinical and biological values of the low and high renin sub-groups of patients with ESRD are shown below:

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The osmotic pressure in plasma decreased in the low and high renin subgroups similarly by about 20 mOsm/kg. Mean arterial blood pressure fell in both subgroups by about 12 mmHg and blood volume decreased significantly by 4.4% (1.1%) and 12.1(1.7) % , respectively in the low renin and high renin subgroups.

PK

Endogenous AVP, Renin and Aldosterone

Hemodialysis

The pre and post dialysis values for AVP, renin and aldosterone are shown in the below table:

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Dialysis had no significant impact on PRA: the post dialysis values in the two subgroups remained statistically significant. The pre- and post- dialysis plasma aldosterone concentrations were significantly higher in the high renin subgroup than in the low renin subgroup. The aldosterone levels were significantly reduced during dialysis in both subgroups.

The mean (SEM) baseline values for endogenous AVP in the healthy subjects and patients with ESRD were 2.2 (0.7) and 21.3 (1.9) pg/mL, respectively. The mean pre-dialysis values for endogenous AVP were 15.2 (2.8) pg/ml and 13.9 (1.0 pg/mL), respectively, in the low and high renin subgroups of the patients. The post-dialysis values for AVP averaged 6.6 (1.2) and 8.7(0.7) pg/mL in the low and high renin subgroups, respectively. The respective, pre- and post-dialysis values and the dialysis related lowering of the AVP concentrations were comparable in the low and high renin subgroups. The reduction in the osmotic pressure during dialysis was also similar for the low and high renin subgroups. The pre- and post-dialysis values from AVP in the patients on antihypertensive medication were not significantly different from those of the other patients.

The below figure showing a linear plot of the plasma concentration of AVP before and after dialysis vs. effective plasma osmolality indicated an apparent linear relationship with a similar slope:

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The renin status appears not to be relevant.

Ultrafiltrate

The mean concentration of AVP in the ultrafiltrate [6.2 (1.2) pg/mL (n=10)] was only slightly lower than the combined mean post-dialysis concentrations in plasma in the low [6.2 (1.2) n=9] and high renin [8.7(0.7) (n=31)] subgroups. This finding indicates that AVP is dialyzable and its plasma protein binding is low. Low protein binding of AVP is supported by comparable concentrations of AVP in plasma and ultrafiltrate in patients undergoing extracorporeal ultrafiltration (2).

Exogenous AVP

The PK parameters of exogenous AVP are tabulated in the below table:

Group	V_{D1}	V_{Dz}	$t1/2_1$	t1/2λz	CL1	CL2
	mL/kg	mL/kg	min	min	mL/kg/min	mL/kg/min
Healthy Subjects	150.6 (25.1)	292.1 (32.1)	7.2 (0.9)	11.2(0.9)	14.3 (1.4)	18.3 (1.9)
ESRD Patients	109.0 (16.0)	174.0 (29.4)*	8.6(1.2)	13.6(1.9)	8.7 (0.8)*	8.9 (0.7)*

* Significantly different in the ESDR patients compared to the healthy subjects

The reported clearance values and the value for VD1 The reduction in clearance appears to be mainly due to a smaller V_D in the ESRD patients without a relevant change in the terminal elimination half-life. Because of the insufficent documentation of the measured plasma concentration time profile of AVP after bolus administration the PK parameters for exogenous AVP must be interpreted with caution.

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusions

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Exogenous AVP The reported results on the parameters of AVP in patients with ESRD and the controls cannot be considered valid because: • Blood samples were not collected frequently enough to determine the plasma concentration time profile of AVP • The data analysis methods used to calculate the PK parameters in the ESRD patients are and the controls are incorrect • The issue of how to correct for the sizable concentrations of the endogenous AVP concentrations is not addressed ***Endogenous AVP*** • The plasma concentrations of endogenous AVP are increased 9.7 fold in ESRD patients relative compared to healthy subjects suggesting a decrease in renal metabolism • The AVP concentrations are linearly correlated with osmotic pressure • Hemodialysis reduces osmotic pressure and endogenous AVP • AVP is dialyzable • The similar plasma and dialysate concentrations indicate low plasma protein binding of AVP
Comments
• None
References 1. Kimura T, Matsui K, Ota K, Yoshinaga K. Radioimmunoassay of arginine vasopressin in human plasma and urine, a resin microcolumn method. Tohoku J Exp Med 1980;13:37-46 2. Shimamoto, K, Ando T, Nakao T, Watari I, Miyhara M. Permeability of antidiuretic hormone and other hormones through the dialysis membrane in patients undergoing chronic hemodialysis. J Clin Endocrinol Metab 1977;45: 818-820

5. PK and PD in Adult Patients with Target Disease: Septic Shock, Post-cardiotomy Shock or Shock of Mixed Etiology

5.1

Report #	**Study Period:** Not indicated	**EDR Link**
Title	Vasopressin Decreases Intestinal Mucosal Perfusion: A Clinical Study on Cardiac Surgery Patients in Vasodilatory Shock. Nygren, A, Thoren A, Rickstein S-E. Acta Anesthesiol Scand 2009;53:581-588	
Study Design: Single group study in 8 mechanically ventilated post-cardiotomy patients with vasodilatory shock receiving sequential 30 min infusions of ascending rates of vasopressin 0.02, 0.04 and 0.08 U/min. The simultaneous infusion rate of norepinephrine (NE) was modified to maintain a mean arterial blood pressure (MAP) of 75 mm Hg. A titration period of 5-15 min was needed for each infusion rate to obtain the target MAP. In		

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the post-intervention period MAP was maintained at 75 mm Hg. The inotropic medication was not changed and additional fluids, except for replacing urine loss were not administered.	
Rationale: Post-cardiotomy vasodilatory shock is characterized by a profound arteriolar vasodilation caused by endogenous vasodilators including nitric oxide, prostaglandins, inflammatory mediators or activation of the ATP sensitive potassium channels in vascular smooth muscle cells, promoted by e.g. lactic acidosis (1,2). Resistance to catecholamines via down regulation of adrenergic receptors may also contribute (3,4). Plasma levels of endogenous AVP are reportedly low in post-cardiotomy vasodilatory shock and in septic shock in contrast to hypovolemic and cardiogenic shock suggesting that this deficit contributes to the development of post-cardiotomy or septic shock (5,6). An increased sensitivity to AVP has been claimed as well (7). Concerns regarding a reduction of splanchnic perfusion and increases in transaminases and total bilirubin in vasodilatory shock have been raised (8,9). To gain more insight of AVP's effect on local gastric and jejunal perfusion ascending doses of vasopressin were infused into patients with post-cardiotomy vasodilatory shock.	
Objectives: Primary: To study the dose-exposure and response profile of ascending doses of vasopressin	
Endpoints: Mean arterial blood pressure, heart rate (HR), cardiac index (CI), central venous pressure (CVP), pulmonary artery occlusion pressure (PAOD), systemic vascular resistance index (SVRI), stroke volume index (SVI), systemic oxygen delivery index (DO_2I), systemic oxygen consumption (VO_2I), systemic oxygen extraction (SO_2 extr), mixed venous oxygen saturation (SVO_2), hemoglobin	
Inclusion Criteria: Mechanically ventilated patients with post-cardiotomy vasodilatory shock who fulfilled the following criteria: MAP < 60 mm Hg despite optimal pre-load as assessed by right- and left sided cardiac filling pressures and transesophageal echocardiography, need for norepinephrine to obtain MAP> 60 mm Hg, CI > 2.5 L/min/m^2	
Exclusion Criteria: Not indicated	
Screening: Not indicated	**Washout:** not applicable
Periods	Not applicable
Treatment: Sequential intravenous infusions of 0.02, 0.04, 0.08 U/min vasopressin	
Sequence	Not applicable
Dose Selection: 0.02, 0.04 and 0.08 U/min AVP are doses previously shown to exert pharmacological effects	
Investigational Drugs and Formulations: Identity and source of the vasopressin infused were not indicated by the publication. However, upon inquiry the authors indicate that Pitressin (Parke-Davis) was administered to the patients	
Administration: Constant rate intravenous infusion of vasopressin for 30 min at each dose level	
Fed/Fasted: Not indicated	
Interfering Substances: milrinone, dopamine, NE for blood pressure support, fentanyl, midazolam for sedation	
PK and PD Sampling Times: Plasma samples of vasopressin were measured at baseline and at the end of each 30 min infusion period and 30 min after stopping the highest	

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infusion rate. Body temperature, MAP, CVP, PAOP, and HR were continuously measured.

Analytical Method

The method used for the determination of vasopressin in serum was not indicated in the publication. However, after inquiry the authors indicate that AVP was extracted in plasma with cold ethanol. The coefficient of variations for intra- and inter-assay variability were <10% and <16%, respectively.

Analyte		Vasopressin
Method		Not indicated
Matrix		Serum
Range, ng/mL		Not indicated
Quality Control	%CV	Not indicated
	%RE	Not indicated

Lactate

The lactate concentrations were measured by an enzymatic method.

PD Methods

Jejunal mucosal perfusion was measured by laser Doppler flowmetry and gastric mucosal pCO2 by tomometry. The hepatic vein was catheterized. Blood gas analyses were performed using an automated blood gas analyzer.

Target PK Parameters: $C_{baseline}$, $C_{30\ during\ infusion}$, $C_{30\ after\ infusion}$

PK Data Analysis: t1/2 calculated from comparing $C_{30\ during\ infusion}$ with $C_{30\ after\ infusion}$

Target PD Parameters: MAP, HR, CI, CVP, PAOP, SVRI, SVI, DO_2I, VO_2I, SO_2 extr, SVO_2, hemoglobin

Statistical Method/Sample Size/Power: The Kolmogorov-Smirnov test for goodness of fit to a normal distribution was used and normality was obtained for all main measurements. ANOVA for repeated measurements and linear trend test were used to evaluate the effects of vasopressin on the measured variables. Pre- and post-infusion values were compared using a paired Student's t-test. Therefore the selected sample size was not based on power considerations.

Results

Study Population:

Randomized	8
Treated	8
Completed	8
Discontinued	0
Pharmacokinetic population	8
Safety population	8
Age [Mean (SD)], years	70(7)
Weight [Mean (SD)], kg	Not indicated
Male/Female	7/1
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated

The clinical characteristics of the patients at study entry are summarized in the below table:

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The interval between cardiotomy and study entry ranged widely between 2 and 19 days. The SOFA scores were in all patients ≥ 9 and all patients suffered from multiple organ failure. Three (3) patients had an identified source of infection (pneumonia or urosepsis). The 5 patients without infection were considered to have post-cardiotomy vasodilatory shock. Four patients received dopamine and 4 patients received intravenous milrinone. All but one patient left the ICU alive. The one patient died of multiple organ failure 10 days after the study.

The mean (SD) serum concentration of vasopressin and associated changes in the pharmacological endpoints are summarized in the below table:

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PK

The mean (SD) endogenous AVP concentration at baseline was 3.1(1.8) pg/mL. The baseline uncorrected mean serum concentrations 30 min after initiation of the infusions calculated by the Reviewer are listed in the below table:

Dose Normalized Mean Concentrations and Clearances of AVP

Reference ID: 3313815

Infusion Rate, U/min	C_{30}, pg/mL	C_{30}Dose Normalized	Clearance, mL/min
0.02	24.0 (7.7)	24.0	1542
0.04	42.8 (12.8)	21.9	1723
0.08	89.0 (23.0)	23.0	1663

The dose normalized C_{30} after infusion rates between 0.02 and 0.08 U/min were constant indicating apparent linear PK of AVP in the patients.

PD

The doses of NE required to maintain MAP > 75 mm Hg during the 3 vasopressin infusions could be significantly reduced. The incremental doses of vasopressin were accompanied by a significant decrease in CI, SVI, DO_2I, and SVO_2. The changes in these parameters tended to increase with the increase in the infusion rate of AVP. The effect of NE on splanchnic perfusion is reportedly negligible (10). Thus, the changes in the splanchnic perfusion observed in this study are attributable to vasopressin.

Splanchnic Perfusion

The effects of the incremental doses of vasopressin on the splanchnic perfusion are shown in the below table and figure:

Increasing doses of vasopressin decreased jejunal mucosal perfusion and increased the arterial-gastric mucosal pCO2 gradient. In contrast, the hepatic blood gas analyses and lactate concentration were not impacted by vasopressin. Pre-and post intervention values of the various splanchnic variables did not differ significantly.

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
-

Conclusion

PK

- The PK of AVP is dose proportional at rates between 0.02 and 0.08 U/min
- The estimated CL ranges between 1542 and 1723

PD

- Increasing doses of AVP decreased jejunal mucosal perfusion and increased the arterial-gastric mucosal pCO2 gradient

Limitations of the study include:

- The interval between cardiotomy and study entry varies significantly among the patients. This may have affected the response to vasopressin
- The protocol prescribed titration of NE to a MAP > 75 mm during the infusions with the incremental doses of vasopressin Hg made it impossible to evaluate the exposure-response relationship of vasopressin.

Reference ID: 3313815

Comments
• None

References

1. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock N Engl J Med2001;345:588-595
2. Parillo JE. Pathogenic mechanisms of septic shock N Engl J Med 1993;328:1471-1477
3. Tsuneyoshi I, Kanmura Y, Yoshimura N. Nitric oxide as a mediator of reduced arterial responsiveness in septic patients Crit Care Med 1996;24:1083-1086
4. Meadows D, EdwardsJD, Wilkins RG, Nightingale P. Reversal of intractable septic chock with norepinephrine therapy. Crit Care Med 1988;16:663-666
5. Argenziano M, Chen JM, Choudhri, AF, Cullinane S, Garfein E, Weinberg AD, Smith Jr CR, Rose EA, Landry DW, Oz MC. Management of vasodilatory shock after cardiac surgery: Identification of predisposing factors and use of a novel pressor agnet. J Thorac Cardiovasc Surg 1998;116:973-980
6. Argenziano M, Choudri AF, Oz MC, Rose EA, Smith CR, Landry DW. A prospective randomized trial of arginine vasopressin in the treatment of vasodilatory shock after left ventricular assist device placement. Circulation 1997;96:II-286-290
7. Landry DW, Levin HR, Gallant EM, Seo S, D'Alessandro D Oz MC, Oliver JA. Vasopressin deficiency contributes to the vasodilation of septic shock [see comments] Circulation 1997;95:1122-1125
8. Duenser MW, Mayr AJ, Ulmer H, Ritsch N, Knotzer H, Pajk W, Luckner G, Mutz NJ, Hasibeder WR. The effects of vasopressin on systemic hemodynamics in catecholamine –resistant septic and post-cardiotomy shock: a retrospective analysis. Anaesthet Analg 2001;93:7-13
9. Luckner G, Duenser MW, Jochberger S, Mayr VD, Wenzel V, Ulmer H, Schmid S, Knotzer H, Pajk W, Hasibeder W, Mayr AJ, Friesenecker B. Arginine vasopressin in 316 patients with advanced vasodilatory shock. Crit Care Med 2005; 33:2659-2666
10. Nygren A, Thoren A, S-E Ricksten. Norepinephrine and intestinal mucosal perfusion in vasodilatory shock after cardiac surgery. Shock 2007;28:536-543

5.2

Report #	**Study Period** : Not indicated	**EDR Link**
Title	Endocrinologic Response to Vasopressin Infusion in Advanced Vasodilatory Shock. Duenser MW, Hasibeder WR, Wenzel V, Schwarz S, Ulmer H, Knotzer H, Pajk W, Friesenecker BE, Mayr AJ. Crit Care Med 2004;32:1266-1271	
Study Design: Preliminary, prospective, randomized, controlled clinical study. Thirty eight (38) critically ill patients with vasodilatory shock after cardiovascular surgery or due to systemic inflammatory response syndrome with and without sepsis with a mean		

Reference ID: 3313815

arterial blood pressure (MAP) of < 70 mm Hg despite adequate volume resuscitation, and norepinephrine (NE) requirements > 0.5 µg/kg/min were prospectively enrolled. If stroke volume index remained < 25 mL/min/m2 or cardiac index < 2 L/min/m^2, a continuous infusion of milrinone was started at doses ranging from 0.3 to 0.6 µg/kg/min. The patients were randomized to receive either AVP/NE or NE alone. AVP was infused at a constant rate of 4 U/h in the AVP/NE group. In NE patients, MAP ≥ 70 mmHg was achieved by adjusting the NE infusion, as necessary. Heart rate (HR), MAP, stroke volume index and NE requirements were recorded at baseline and 1, 12 and 24 h after randomization.

Rationale: Only limited data exist on the effects of AVP on other hormones

Objectives: Primary: To evaluate the endocrinologic response to combined a AVP/NE infusion in advanced shock, and to examine the relationship between plasma AVP concentrations and the hemodynamic response

Screening: Not indicated	Washout: not applicable
Periods	Not applicable

Treatment: AVP+NE or NE

Sequence	Not applicable

Dose Selection: Infusion of AVP at 0.067 U/min is in the middle of the range of doses considered pharmacologically effective and safe.

Investigational Drugs and Formulations: Pitressin (Parke-Davis) synthetic AVP and NE. The trade name of the NE used is not provided

Administration: Constant intravenous infusion

Fed/Fasted: Not indicated

Interfering Substances: only NE indicated

PK Sampling Times: Blood samples were collected at baseline and 12 and 24 h after randomization. AVP, ACTH, cortisol, angiotensin II, aldosterone, prolactin, endothelin I and atrial natriuretic factor were determined.

PD Sampling Times: At baseline and 1, 12 and 24 h after randomization

Analytical Method

After centrifugation the samples were stored at – 80 ◦C.

Analyte		AVP
Method		RIA
Matrix		Plasma
Range, ng/mL		Not indicated
Quality Control	%CV	Not indicated
	%RE	Not indicated

Blood samples were centrifuged and plasma stored at -80 ◦C until assaying. AVP was measured after extraction with ethanol using a RIA method. No additional information on the RIA used is provided by the publication. The other hormones were measured by RIA or enzyme-immunoassays.

Target PK Parameters: CL

PK Data Analysis: CL=ko/C24h and CL=ko/C48h

Target PD Parameters: Change in plasma concentrations of target hormones and MAP,

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HR and stroke volume index (SVI) and NE requirements

PK-PD Analysis: Regressions of ΔMAP, HR, SVI and NE dose requirements on the plasma concentrations of AVP at baseline were performed

Statistical Method: Continuous demographic and clinical data were compared if Gaussian distributed with independent sample student's t-tests (age) and if non-Gaussian distributed with Mann-Whitney U rank sum test. Categorical data were compared with the use of the chi-square (gender, diagnosis, intensive care unit mortality). To evaluate differences in hormonal plasma concentrations between study groups linear mixed effects models were used to account for death related drop-out. The relationship between plasma concentrations and of AVP and the hemodynamic response to AVP infusion (changes from baseline in MAP at 1 and 24 h. HR, stroke volume index, and NE dose requirements at 24 h) was analyzed using a linear regression model. Shapiro-Wilks tests were used to check for normality of distribution, which was fulfilled in all variables except for prolactin plasma concentrations at baseline. After log transformation normality of the distribution for the prolactin plasma concentrations was achieved.

Sample Size/Power: The study is to provide preliminary information. Therefore, the selected sample size is not based on power considerations.

Results

The characteristics of the patients are listed in the below table:

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Of note the etiology of the vasodilatory shock was sepsis, systemic inflammatory response syndrome and status after post-cardiotomy.

Study Population:

Randomized	38
Discontinued	12
Treated with AVP +NE	19
Completed	Not indicated
Discontinued	Not indicated
PK and PK-PD population	19
Safety population	19

Treated with AVP +NE Completed Discontinued PK and PK-PD population Safety population	19 Not indicated Not indicated 19 19
Weight [Mean (SD)], kg	Not indicated
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated

PD

The changes in the plasma concentrations of the hormones are listed in the below table:

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Apart form the expected increase in AVP the infusion of 0.067 U/min AVP increased only the plasma levels of prolactin significantly by factors of 21 and 18 at 24 and 48 h after initiation of the infusion, respectively.

PK

On the assumption that the plasma concentrations 24 and 48 h into the infusions reported for AVP refer to the 19 patients of the NE+AVP group the Reviewer estimated that the CL of AVP in the patients at 24 h and 36 h was 692 and 781 mL/min, respectively.

PD and PK-PD

The regression of the target parameters on the baseline plasma concentrations of AVP in the group receiving AVP+NE are shown below. The first figure shows that in all 19 individuals MAP increased relative to baseline 1 h after initiation of the infusion:

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In all 19 patients MAP increased relative to baseline. However, there is significant inter-subject variation (5.1- 41.0 mm Hg).

The next four figures show the changes in MAP, HR, SVI and NE dose requirements during the 24 h interval after initiation of the infusion vs the baseline plasma concentrations of AVP:

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The changes observed for MAP after 1 h into the infusion or for MAP, HR, SVI or NE dose requirements during the 24 h interval after initiation of the infusion appear not to depend on the baseline plasma concentrations of AVP. In 18 of the 19 patients receiving the NE+AVP regimen MAP is elevated at 1 h and during the 24 h after start of the infusion. Fifteen (15) patients show a reduction in HR, 13 an increase in SVI and 18 a reduction in the NE dose requirements relative to baseline during the 24 h interval after initiation of the infusions of NE and AVP.
Safety
▪ Was there any death or serious adverse events? ☑ Yes ☐ No ☐ NA No details on safety and cause of deaths of the patients are provided in the publication
Conclusion
PK • The estimated CL values of AVP in the patients receiving the NE+AVP infusions are 781 and 692 mL/min. The respective coefficients of variation about the mean concentrations of AVP are **PK-PD** • The respective effects of AVP on MAP, HR, SVI and NE dose requirements are not related to the baseline concentrations of AVP • 95% of the patients on NE+AVP show an increase in MAP at 1 h and lasting 24 h after start of the infusion. • 79 % of the patients show an decrease in HR, 68% an increase in SVI and 95% a reduction in the NE dose requirements during the 24 h after initiation of the infusions with NE +AVP Limitations of the study include: • The relationship between the total (exogenous + endogenous) AVP concentration and the hemodynamic parameters 24 and 48 h into the infusions were not evaluated.
Comments
• None

6. PD in Patients with Target Disease: Septic Shock

6.1

Report #	**Study Period:** Not indicated	**EDR Link**
Title	Low-Dose Vasopressin in the Treatment of Vasodilatory Septic Shock. Malay MB, Ashton RC, Jr, Landry DW, Townsend RN. Journal of Trauma: Injury, Infection, and Critical Care 1999;47:699-705	
Study Design: Randomized, double-blind, placebo controlled study in 10 patients with severe septic shock		
Rationale: Preliminary studies have shown that AVP may be useful in the treatment of vasodilatory shock. However, only a randomized, controlled study can definitively assess benefits and risk associated with the treatment of a new pharmacological entity.		

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Objectives: Primary: To determine hemodynamic effects of a low dose of AVP Secondary: To determine adverse events	
Endpoints: Primary: To determine the hemodynamic response as defined by an increase in arterial blood pressure. Secondary: Time to catecholamine free hemodynamic stability defined as mean arterial blood pressure (MAP) > 70 mm Hg for > 30 min in the absence of any known vasopressor agent except the study drug and/or a low dose dopamine infusion (3 μg/kg/min) and averse events, including bradycardia, arrhythmias, myocardial and/or mesenteric ischemia or infarction and death	
Inclusion Criteria: Patients in the age > 18 years with a diagnosis of septic shock defined in accordance with the American College of Chest Physicians/Society of Critical Care Medicine Consensus Committee, including suspected infection or positive blood cultures, mechanical ventilation and at least one or more of the following: Heart rate (HR) > 90 bpm, temperature >38 º C or < 36 º C, white blood cells >12 000 cells/mm^3 or < 4000 cells/m^3 (or >10% immature forms), systolic arterial blood pressure < 90 mmHg or a reduction of > 40 mm Hg from baseline persisting, despite fluid resuscitation and at least one sign of organ dysfunction (PaO2/FiO2 ratio < 250, serum creatinine >2.0, or need for dialysis to regulate serum potassium and bicarbonate, bilirubin > 2.0 or elevation of transaminases to twice normal, Glasgow Coma scale score < 9, platelet count < 50 000 or an elevation of prothrombin time to twice normal in the absence of anticoagulans. In addition all patients had vasodilatory hypotension defined as cardiac index (CI) > 2.5 L/min and a mean arterial blood pressure (MAP) < 70 mm Hg, despite the use of conventional vasopressor agents (dopamine > 3 μg/kg/min and any dose of epinephrine, norepinephrine and/or phenylephrine) initiated after fluid replacement. Because several patients were referred into the study after initiation of the vasopressor therapy, a minimal pulmonary capillary wedge pressure (PAOP) of 12 mm Hg at study entry was chosen to reflect that at least adequate attempts had been made at volume replacement before initiation of catecholamine agents.	
Exclusion Criteria: Pregnant women, patients with electrographic or enzymatic evidence of ongoing myocardial ischemia or infarction or those with suspected mesenteric ischemia/infarction	
Screening: Not indicated	**Washout:** Not applicable
Periods	Not applicable
Treatment: AVP or saline	
Sequence	Not applicable
Dose Selection: 0.04 U/min	
Investigational Drugs and Formulations: AVP (Pitressin®, Parke-Davis). The publication does not indicate that AVP was dissolved in isosaline.	
Administration: Constant rate intravenous infusion	
Fed/Fasted: Not indicated	
Interfering Substances: Not indicated	
PK Sampling Times: Blood samples for the determination of AVP were not collected	
PD Sampling Times: At Baseline and 1, 4, 12 and 24 h after study drug administration	
Analytical Method: Not applicable	
Target PK Parameters: Not applicable	
PK Data Analysis: Not applicable	
Target PD Parameters: MAP, systolic blood pressure (SBP), heart ate (HR), pulmonary artery occlusion pressure (PAOP), cardiac index (CI), systemic vascular resistance (SVR), oxygen delivery (DO2), catecholamine requirements	
Statistical Method/Sample Size/Power: Hemodynamic variables before and 1 h after	

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study drug administration were compared using Student's paired t-test. Hemodynamic variables and vasopressor dosages between groups were compared using a two-way analysis of variance for repeated measures. Changes within groups over time were compared with baseline values using a one way analysis of variance for repeated measures. Differences in laboratory values at 24 h after study drug administration were compared with baseline values using a paired t-test. The goal of the study is to provide preliminary information. The selected sample size was not based on power considerations.

Results

Study Population:

Randomized		10
Treated with AVP		5
Completed		5
Discontinued		5
Pharmacodynamic population		5
Safety population		5
Treated with Saline		5
Completed		3
Discontinued		2[a]
Pharmacodynamic population		5
Safety population		5
Age [Mean (SEM)], years	AVP	53(10)
	Saline	56(7)
Weight [Mean (SEM))], kg	AVP	88 (8)
	Saline	91(10)
Male/Female	AVP	4/1
	Saline	4/1
Race (Caucasian/Black/Hispanic/ Asian/Other)	AVP	Not indicated
	Saline	Not indicated

[a] Two patients died before the 24 h time point. One patient died 8 h after study drug initiation and one patient died 18 h after study drug initiation

The mean (SEM) hemodynamic data and catecholamine requirements at study entry of the patients and the cause of septic shock are shown in the below two tables:

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With the exception of a statistically significant difference in CI the baseline characteristics in the two groups were comparable. It appears that not all patients exhibited a MAP < 70 mm Hg at baseline.

The mean (SEM) hemodynamic variables at baseline and 1 h after initiation of study drug are shown in the next table:

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Treatment with AVP resulted in significant elevations in MAP, SBP and SVR relative to baseline. The results suggest that the increase in MAP was secondary to AVP's effect on SVR. In contrast, treatment with saline resulted in no change in the hemodynamic variables relative to baseline.

The hemodynamic variables and catecholamine requirements 24 h after study drug initiation are shown in the next table:

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Two patients in the placebo group died before the 24 h time point. Both deaths were attributable to refractory hypotension (MAP < 70 mmHg). Because of the limited sample size of the placebo group valid statistical group comparisons to evaluate the secondary endpoint of reduction and withdrawal of catecholamines were not possible.

Treatment with AVP allowed a reduction in catecholamine requirements. At 24 h, all standard vasopressors in the AVP group could be withdrawn. However, AVP could be withdrawn successfully only in one of the 5 subjects. In the other 4 patients' withdrawal of AVP resulted in a decrease of MAP to values < 70 mm Hg and required reinstitution of AVP at a rate of 0.04 U/min.

As shown in the below table within each group there were no significant differences in the values at baseline and 24 h:

Safety

- Was there any death or serious adverse events? ☑Yes ☐ No ☐ NA

Two patients receiving the saline died due to refractory hypotension. No adverse cardiac ischemia or episodes suggestive of mesenteric ischemia, infarction or both were observed.

Conclusions

- A 1 h infusion of AVP at a rate of 0.04 U/min increases mean MAP significantly from 65 mmHg to 80 mm Hg in patients with septic shock, whereas saline infused at the same rate had no impact on MAP.
- AVP, in contrast to placebo, reduced the catecholamine requirements 24 h after initiation.
- Two patients receiving the saline died due to refractory hypotension. No adverse cardiac ischemia or episodes suggestive of mesenteric ischemia, infarction or both were observed in either group.
- Limitations: Small number of subjects enrolled. The interval between diagnosing shock and study drug initiation is not stated. Differences in the time interval between groups could affect outcomes.

Comments

Reference ID: 3313815

• None

6.2

Report #	Study Period: July 2001- April 2006 in 27 centers in Canada, Australia, and the USA.	EDR Link
Title	Vasopressin Versus Norepinephrine Infusion in Patients with Septic Shock, the Vasopressin and Septic Shock Trial (VASST) and Supplementary Appendix. Russell JA, Walley KR, Singer J, Gordon AC, Hebert P, Cooper JD, Holmes CL, Mehta S, Ranton JT, Storms MM, Cook DJ, Presneill JJ, Ayers D, for the VASST Investigators and Supplementary Appendix. New Engl J Med 2008, 358: 877-887, Interaction of Vasopressin Infusion, Corticosteroid Treatment, and Mortality of Septic Shock. VASST Investigators Cri Care Med 2009;37:811-818	

Study Design: Multi-center, randomized, stratified, double-blind trial with assignment of patients with septic shock and receiving a minimum of 5 µg/min norepinephrine (NE) to receive either low-dose vasopressin (0.01-0.03 U/min) or NE (5-15 µg/min) in addition to open label vasopressors. The subjects were stratified for severity of septic shock. Severe septic shock patients received ≥15 µg/min vasopressin (AVP). Patients with less severe septic shock received 5-14 µg/min NE. During the initiation and titration of the study drugs, the bedside nurse also titrated open-label vasopressors to maintain a constant target mean arterial pressure. The initial target mean arterial blood pressure (MAP) was 65-75 mm Hg, however, the attending physician could modify the target blood pressure. Vasopressors were titrated and tapered according to protocol to maintain a target blood pressure. Open-label vasopressors were only increased if the target mean arterial blood pressure was not reached on maximal study drug infusion. Tapering of open-label vasopressor was permitted only when the target mean arterial blood pressure had been reached during study drug-infusion. Tapering of the study drug was only permitted when the target mean arterial blood pressure had been maintained for 8 h without any open-label vasopressors. Infusion of AVP at 0.03 U/min was continued until the patient died, a serious adverse event occurred, or the patient's condition improved to the extent that open-label vasopressors were no longer required. Neither crossover to the other group or open-label AVP was permitted. Study drug infusion was discontinued or interrupted if any of the following predetermined serious adverse events occurred: acute ST-segment elevation confirmed by a 12 Lead ECG, serious or life threatening cardiac arrhythmias, acute mesenteric ischemia, digital ischemia, or hyponatremia (serum sodium <130 meq/L). Study drug was discontinued if for at least 8 h if the adverse event was judged to be drug related. In that case a serious adverse event was recorded. The study drug could be restarted if in the judgment of the investigator or attending physician the adverse event had been treated, the condition was reversed and the event was thought not to be caused by the study drug or protocol. If vasopressor support was required after a patients had been weaned from the study drug, the study drug was preferentially re-infused, as long as no exclusion criteria were met.
In a subgroup of patients blood samples for the determination of plasma concentrations of

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vasopressin were collected at 6 sites.	
Rationale: Despite the widespread use of vasopressin only two small randomized trials investigated the impact of vasopressin in septic shock. However, neither of the trials was powered to evaluate mortality, organ dysfunction, or safety. To address these uncertainties the present trial was performed.	
Objectives: Primary: To determine whether vasopressin reduces the 28 day mortality of patients with septic shock and are receiving the usual care (including catecholamines) as compared to NE. Secondary: to determine whether the beneficial effects of vasopressin are more pronounced than those of NE in patients with in the subgroup of patients with more severe septic shock.	
Screening: 6229 patients	**Washout:** Not applicable
Periods	Not applicable
Treatments: 5-15 μg/min NE infusion vs. 5-15 μg/min NE plus 0.01-0.03 U/min vasopressin infusions targeted to maintain MAP between 65-75 mmHg in patients on 5 μg/min NE in septic shock	
Sequence	Not applicable
Dose Selection: Vasopressin at infusion rates of between 0.01-0.03 U/min have been postulated to exhibit hemodynamic effects and to be safe.	
Investigational Drugs and Formulations: Source and identity of the infused arginine vasopressin is not indicated in the publication.	
Administration: AVP (30 U) and NE (15 mg) were mixed in identical 250 mL intravenous bags of 5% dextrose in water. The blinded AVP infusion were started at 0.01 U/min and titrated to a maximum of 0.03 U/min, whereas the blinded NE was started at 5 μg/min and titrated to a maximum of 15 μg/min. In severe septic shock the infusion rate of NE could also exceed 15 μg/min. The infusions were prepared by study pharmacists who were aware of the two treatments. All other clinical staff, research personnel, patients, and families were unaware of the treatment assignments for the duration of the trial.	
Inclusion Criteria: Patients > 16 years of age with septic shock resistant to fluid s (as defined by lack of response to 500 mL normal saline or a requirement for vasopressors and low dose NE. Septic shock was defined by the presence of two or more diagnostic criteria for the systemic inflammatory response syndrome, proven or suspected infection, new dysfunction of at least one organ, and hypotension despite adequate fluid resuscitation (requiring vasopressor support of > 5 μg or the equivalent/min).	
Exclusion Criteria: Unstable coronary syndrome, > 24 h elapsed since patient met entry criteria, us of open-label vasopressin for blood pressure support during current hospital submission, malignancy or other irreversible disease or condition with estimated 6 month mortality ≥ 50%, acute mesenteric ischemia (proven or suspected), death anticipated with 12 h, chronic heart disease (NYHA Class III or IV), physician or team not committed to aggressive therapy, serum sodium < 130 mEq/L, traumatic brain injury, Raynaud's phenomenon, systemic sclerosis or vasospastic diathesis, pregnancy	
Endpoints: Primary: The primary endpoint was death from any cause and was assessed 28 days after the start of infusions. Secondary: 90 day mortality, days alive and free of organ dysfunction during the first 28 days, days alive and free of vasopressor use, mechanical ventilation, or renal replacement therapy; days alive and free of the systemic inflammatory	

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response syndrome, defined as freedom from two or more of the four diagnostic criteria for the systemic inflammatory response syndrome, days alive and free of corticosteroid use, and length of stay in the ICU and hospital. The rate of the occurrence of serious events was also evaluated.
Fed/Fasted: Not indicated
Interfering Substances: Not indicated
PK Sampling Times: Pre-dose. 6, 24, 72 and 168 h after initiation of study drug infusion
PD Sampling Times: No indicated
Analytical Method Vasopressin was analyzed after extraction on reverse phase column by double antibody immunoassay (Buehlmann Laboratories, Basel Switzerland) at London Laboratory Services Group, London, Ontario). Blood samples were collected into chilled EDTA bottles, cold centrifuged and the plasma stored at -70˚ C. The sensitivity limit of the assay is 0.39 pmol/L. The intra-assay precision is 11% at a mean plasma concentration of 1.0 pmonl/L, 9.1 % at 10.2 pmol/L and 8.6% at16.5 pmol/L. The inter-assay precision was lower at all levels.
Target PK Parameter: Css
PK Data Analysis: CL=ko/Css where ko is the infusion rate, Css is the median plasma concentration of exogenous AVP measured 6 h after start of the vasopressin infusion.
Statistical Method/Sample Size/Power: Calculation showed that 776 patients were required to enroll, receive the drug to detect a 10% difference in mortality, assuming a mortality rate of 60% in the norepinephrine group and a two sided alpha error of 0.05 and a power of 80%. Two pre-planned interim analyses, after 194 patients had been enrolled and after 388 patients had been enrolled. After both interim analyses, the data and safety monitoring committee recommended continuation of the study without protocol modification. The comparison of the 28 day mortality among the 2 groups used an unadjusted chi-square test. Results are presented as absolute and relative risks and 95% confidence intervals. Kaplan-Meier curves for the estimated probability of survival in the two treatment groups as a function of time from enrollment in the study were compared using the log-rank test. To account for any imbalance between the two treatment groups at baseline, a logistic regression procedure and significant covariates that predicted outcomes were used to adjust the raw values for 28 day mortality. Age, illness severity, Acute Physiology and Chronic Health Evaluation (APACHE II) score at baseline, serious co-existing conditions, and other baseline covariates that predicted outcome were entered into the model. Results are presented as odds ratios and 95% confidence intervals. Parametric procedures (independent t-test), nonparametric procedures (Wilcoxon rank-sum test), or Fisher's exact test were used to compare all secondary outcomes. Patients were also assessed in accordance with the strata of more or less severe septic shock. Using the chi-square test. Logistic regression was used to test the interaction between treatment and stratum. The data analyst and investigators remained blinded during the analysis of the data.
Results

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Study Population:

Randomized	779
Assigned to NE	396
Received infusion	383
Withdrawal of consent	1
Completed and assessed	382
Assigned to vasopressin	406
Received infusion	398
Withdrawal of consent	1
Lost to follow-up	1
Randomized	396
Pharmacokinetic population	107
Safety population	778

The baseline characteristics of the two groups are listed in the below table:

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The patients were severely ill as indicated by the APACHE II scores, the proportion of new organ dysfunctions, serum lactate levels and NE infusion rates at entry

PK

The below figure shows the median (inter-quartile range) plasma concentrations of vasopressin for the group who had received the vasopressin infusions and the group receiving the NE infusion:

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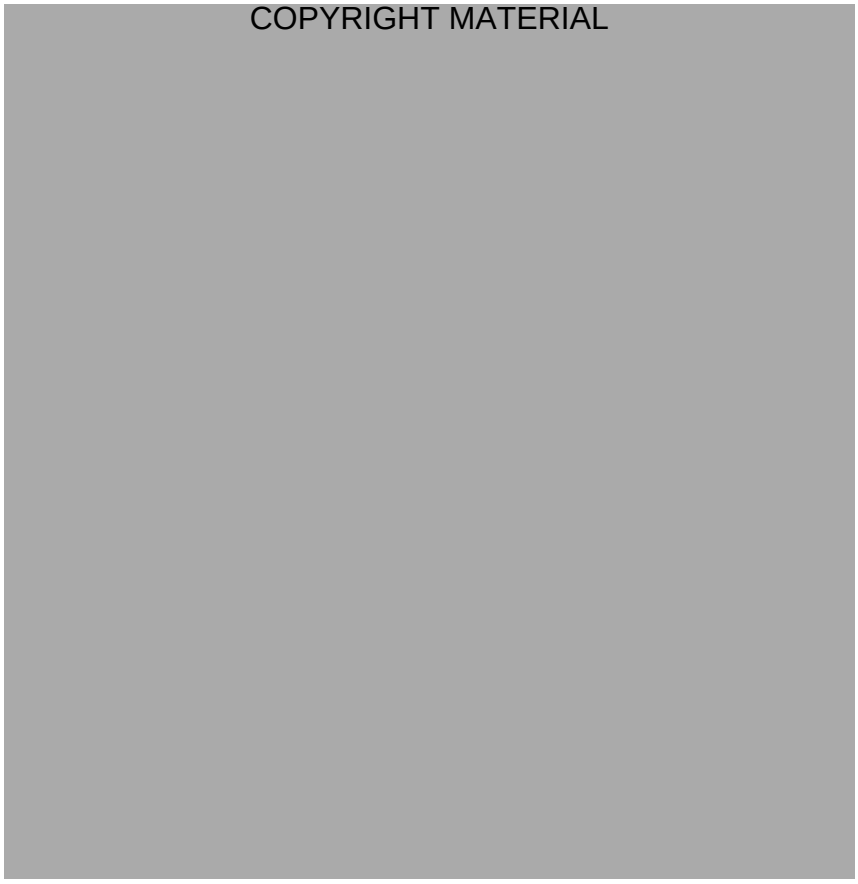

The median plasma concentrations of AVP after a 6 h infusion of 0.03U/min (55600 pg/min) read off the above figure is 73.6 pmol/L. The estimated median clearance of AVP in the patients with septic shock is 755 mL/min.

PD

As shown in the below figures MAP was comparable with the two treatments, whereas heart rate was significantly lower for the first 4 days after initiation of the infusion treatments with vasopressin:

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Relative to baseline MAP in the vasopressin group increased by 1 mm Hg and in the NE group by 2 mm MAP after 4 h infusion (data read off the above figure).

The rate of the NE infusion was significantly lower in the vasopressin group than in the NE group during the first 4 days as shown in the below figure:

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As shown in the below table and figure there was no difference between the groups in the primary outcome, 28 day mortality rate (35% for AVP and 39 % for NE):

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Similarly, there was no significant difference between the groups for 90 day mortality: The results remained non-significant after multivariate regression analysis.

The patients with less severe septic shock showed trends in favor of vasopressin for the group with less severe shock as shown in the below table:

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However, there was no significant difference for 28 and 90 day mortality between patients receiving AVP or NE.

Safety

- Was there any death or serious adverse events? ☑Yes ☐ No ☐ NA
- The overall rates of serious adverse events were approximately 10% each in the AVP and NE groups. Of 11 cardiac arrest reported, 8 occurred in the NE and 3 in the AVP group. Other reported adverse events included decreased cardiac output, mesenteric ischemia, hyponatremia (with vasopressin), skin necrosis and digital ischemia requiring surgery.

Conclusion

PK

- The estimated median clearance of AVP in the patients with septic shock is 755 mL/min. This on the assumption that Pitressin® (Parke-Davis) was infused to the patients in the study.

PD

- There is no difference between the groups assigned to the vasopressin treatment and the group assigned to the NE treatment in 28 or 90 day mortality rate
- Rekative to baseline MAP over time increases comparably with the two treatments, whereas heart rate is significantly lower with the AVP treatment for the first 4 days after initiation of the treatments. These results indicate that AVP raises MAP and compared to NE reduces heart rate.
- The rate of the NE infusion is significantly lower in the AVP group than in the NE group during the first 4 days.
- The overall rates of serious adverse events were approximately 10% each in the AVP and NE groups. Of 11 cardiac arrest reported, 8 occurred in the NE group and 3 in the AVP group.

Limitations

- AVP was infused over a set of doses and the dose and duration of the infusions were not informed by the measured plasma levels of AVP.
- The mean time from meeting the criteria for study entry to infusion of the study drug (12 h) was greater than the period others have postulated to be critical in early

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goal-directed therapy (6) which may be one reason a benefit of AVP over NE was not found by this study. • Because of an incompatibility of AVP with 5% dextrose, the effective dose administered was lower than indicated. Degradation of AVP is about 74% in 6 h and at later times the degradation rate decreases significantly. The infusion rate was 0.03 so that by 6 h into the infusion the rate of AVP is reduced to 0.022 U/min and by 12 h to about 0.018 U/min. At 12 h a new infusion is started and the infusion rate starts to drop over the next 12 h as during the first cycle.
Comments
None

6.3

Report #	**Study Period** :August 2000- -June 2004	**EDR Link**
Title	Vasopressin or Norepinephrine in Early Hyperdynamic Shock. Lauzier F, Levy B, Lamarre P, Lesur O. Intensive Care Care Med 2006;32:1782-1789	
Study Design: This was a prospective randomized, open label, parallel group study conducted in patients with septic shock in 2 centers in Canada and France. The randomized patients received either AVP or norepinephrine (NE). The other vasopressors were tapered and weaned as the experimental drugs were increased. When the maximal dosage of the experimental drugs was attained (AVP 0.04-0.20 U/min, NE 2.6 µg/kg/min administration of the other drugs (AVP or NE) was allowed as rescue therapy if the mean arterial blood pressure (MAP) was still < 70 mm Hg. Dobutamine was used if the cardiac index (CI) decreased below 3 L/min/kg/m^2 within 24 h after randomization. Colloids or crystalloids were used to maintain PAOP >12 mm Hg. Within 24 h after randomization an ACTH stimulation test was performed in all patients with injection of 250 µg ACTH and by measuring cortisol before and 30 and 60 min after injection. Relative adrenal insufficiency was defined as a response of ≤ 9 µg/dL. Non-responders and chronic corticoid steroid users were treated with hydrocortisone 50 mg intravenously every 6 h for at least 1 week. Antibiotic use, surgical management of infection, insulin, sedation, analgesia, transfusions, and other supportive measures were at the discretion of the ICU team.		
Rationale: To date no trial has examined the value of AVP as part of early management of hyperdynamic septic shock. The purpose of this study was to evaluate the effects of AVP on MAP, other hemodynamic and organ dysfunction variable when AVP is used to replace NE in the early resuscitation phase.		
Objectives: Primary: To date no particular vasopressor has been shown to be superior in the early resuscitation phase of septic shock in improving clinical outcome.		
Endpoints: By implication the hemodynamic variable included MAP, heart rate (HR), CI, mean pulmonary artery pressure (MPAP), stroke volume index (SVI) , central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP) systemic vascular resistance index (SVRI) , peripheral vascular resistance index (PVRI) and organ dysfunction variables lactate, mixed venous O_2 saturation, indexed O_2 delivery, indexed O_2 consumption, modified Sequential Organ Failure Assessment (SOFA) score, PaO_2/FIO2 ratio, where FI is the fraction of inspired O_2, creatinine clearance, daily urine output, bilirubin, alanine transaminase, platelet count, gastric arterial difference PCO_2 mm Hg (=$PrCO_2$-$PaCO_2$)		

Reference ID: 3313815

Inclusion Criteria: Meeting criteria for septic shock in accordance with American College of Chest Physicians/Society of Critical Care Consensus Conference and to display at some point a mean arterial blood pressure (MAP) ≤ 60 mm Hg, after at least a 1000 mL crystalloid bolus, on vasopressors for ≤ 12 h before randomization, PAOP ≥ 12 mm Hg and CI ≥ 3 L/min/m^2	
Exclusion Criteria: Patients < 16 years of age, on intermittent dialysis, not expected to live longer than 48 h and pregnant	
Screening: Not indicated	**Washout:** Not applicable
Periods	Not applicable
Treatment: AVP or NE bitartrate infusion at respective rates of 0.04-0.20 U/min and 0.1-2.8 µg/kg/min)	
Sequence	Not applicable
Dose Selection: Not indicated	
Investigational Drugs and Formulations: AVP Ferring (Toronto, Canada), norepinephrine bitartrate, Sabex, Boucherville, Quebec). Publication does not state that AVP was dissolved in isosaline for infusion.	
Administration: Intravenous infusion	
Fed/Fasted: No enteral nutrition was permitted during the first 24 h and was discontinued 8 h prior to the last tonometric measurement at 48 h.	
Interfering Substances: Not sated	
PK Sampling Times: No blood samples were collected for determining AVP plasma concentrations	
PD Sampling Times: The hemodynamic variables were measured pre-dose, 1, 6, 12, 24 and 48 h after protocol initiation. The organ dysfunction variables were measured pre-dose and 12, 24 and 48 h into the infusions.	
Analytical Methods: Not indicated	
Target PK Parameters: Not applicable	
PK Data Analysis: Not applicable	
Target PD Parameters: Heart rate (HR), MAP, CI, SVI, CVP, PAOP, SVRI, gastric tonometry, organ dysfunction parameters	
Target Safety Parameters: Acute coronary syndrome (increase of troponin I above the normal threshold in combination with ST-segment elevation or depression of ≥ 1 mm or T inversion of ≥ 2 mm), arrhythmia, clinically significant gut and skin ischemia	
Statistical Method/Sample Size/Power: Normality was assessed by the Shapiro-Wilks test. Baseline characteristics were evaluated using the unpaired Student's t-test for quantitative variables and Fisher's exact test for categorical variables. The Dunnett's method for comparison with the baseline values when time effects were significant. For non-parametric variables (vaso-active drug requirements and alanine transferase levels) the Kruskal-Wallis test for comparisons within groups and the Mann-Whitney's U test with Bonferroni's adjustment for comparisons between pairs were used. Differences between groups were analyzed by linear mixed effects model to consider death related drop-outs. The goal of the study is to provide preliminary information. Therefore the selected sample size is not based on power considerations.	
Results	
Study Population:	

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Twenty-three subjects were enrolled and 13 and 10 were randomized to receive AVP and NE infusions, respectively, as shown below:

	Treatment	
	AVP	NE
Treated	13	10
Completed	10	7
Died	3	3
Safety population	13	10

Three (3) patients died in both groups, 3 patients during the study protocol, 2 receiving AVP, 1 receiving NE. Death was attributed to refractory shock.
The baseline characteristics of the two treatment groups listed below indicate no significant difference between the 2 groups:

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The volumes of resuscitation fluids administered to the patients in the two groups were comparable.

PD

All patients were < 12 h in septic shock when the infusion regimens were initiated.

<u>Hemodynamics</u>

The results of the evaluation of the hemodynamic variables are listed in the below table:

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Of note the mean baseline value of MAP is 72 mm Hg, violating the inclusion criteria. Relative to baseline MAP increased over time in both groups but differed statistically significantly only 24 and 48 h into the infusions. No difference was observed between groups. A transient decrease in CI lasting from 1 - 12 h into the infusion was only seen in the AVP Group. Also, an increase in SVRI lasting during the entire observation period was seen in the AVP Group. In addition, there was a decrease in O_2 delivery at 48 h in the AVP group. The NE dosage requirements in the AVP Group were lower than in the NE group as shown in the below table:

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However, 85% of the patients on AVP received NE at some point because their MAP was < 70 mmHg despite administration of AVP at the highest infusion rate of 0.2 U/min. No patient in the NE Group received AVP. Three patients in both groups required dobutamine.

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Organ Dysfunction Variables

The below table summarizes the results on the organ dysfuction variables:

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The modified SOFA score was significantly smaller 48 h and the creatinine clerance significantly greater 24 h after initiation of the infusions in the AVP Group compared to the NE Group.

Safety

- Was there any death or serious adverse events? ☑Yes ☐No ☐ NA

Three (3) patients randomized to AVP and 3 patients randomized to NE died. Three (3) patients, 2 in the AVP Group, 1 in the NE Group, died during the study protocol. Death was attributed to refractory shock. One case of acute coronary syndrome occurred in each group, with a maximal troponin I level of 0.8 µg/mL and 0.6 µg/mL in the AVP and NE Groups, respectively. The patient in the NE Group had stable coronary artery disease. Angiography in the patient in the AVP Group revealed occlusion of a small marginal artery. The ST segment depression disappeared in the patient after the AVP infusion rate was reduced from 0.2 to 0.04 U/min. None of the patients developed Q waves or an increase in creatine kinase levels.
The time of death and the acute coronary syndrome relative to the initiation of the AVP and NE infusions was not stated by the publication.

Conclusion

- NE and AVP appear to increase MAP slightly in the first 48 h after administration.
- AVP appears to be able to increase creatinine clearance more than NE.
- The dose requirements of NE are smaller when supplemental AVP is administered.
- An acute coronary syndrome is observed in 2 patients, one on AVP and the other on NE. The patient on AVP receiving 0.2 U/min had stable coronary disease. Three

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(3) patients in each group died from refractory septic shock. • There is no evidence for a tachyphylaxis of the pressor effect of AVP. • The limitations of the study: • The open-label design and small number of subjects enrolled • The MAP in the AVP group exceeds 70 mm Hg • The co-administration regimens of dobutamine are not identical between the treatment groups complicating the comparison of the AVP and NE effects, • All drugs are titrated to attain and maintain a MAP of 70 mm Hg making it challenge to delineate the time course of the effect of AVP on hemodynamics and organ dysfunction variables
Comments
• None

6.4

Report #	**Study Period**: October 1,2004-August 31, 2005	**EDR Link:**
Title	Lack of an Effect of Body Mass on the Hemodynamic Response to Arginine Vasopressin During Septic Shock. Lam SW, Bauer SR, Cha S, Oyen LJ. Pharmacotherapy 2008;28:591-599	
Study Design: Retrospective medical record review of all intensive care units of a tertiary medical center (Mayo Clinic, MN). Mechanically ventilated patients with septic shock receiving a fixed dose intravenous infusion of AVP at 0.04U/min for 6 h as the sole agent for hemodynamic support. The patients were identified from a computer database and screened for inclusion. The patients' electronic medical records were retrospectively evaluated and baseline data on age sex, height, weight, primary service, and concomitant drugs obtained. Concomitant drugs that could have impacted the patients' vasopressor response including β-blockers, amiodarone, drotrecogin alfa, opioids, sedatives, paralytics, parenteral nutrition, and regular human insulin infusions were also recorded. Concomitant catecholamines or inotropic agents started after the initial 6 h of the AVP infusions were also noted. Corticosteroids initiated during the AVP infusions were evaluated in terms of type and duration of therapy.		
Rationale: AVP is often administered at a fixed infusion rate. If the effect is concentration dependent, inter subjects variability should affect hemodynamic stability.		
Objectives: Primary: To determine whether vasopressin (AVP) infused at a fixed infusion rate in patients is more effective in subjects with smaller body mass than in patients with larger body mass.		
Endpoints: Primary: Hemodynamic stability defined as the proportion of patients achieving a mean arterial blood pressure (MAP) of ≥ 65 mmHg without the catecholamine therapy **Secondary:** attainment of hemodynamic stability at 6 h, a change in BP at 1 and 6 h after onset of AVP without catecholamine therapy, length of stay, as well as mortality rate at the time ICU discharge, in the hospital, and at 28 days, the magnitude of MAP at 1 h, and the need for additional rescue vasopressors.		
Screening: Not applicable	**Washout:** Not applicable	

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Periods	Not applicable
Treatment: Intravenous administration of AVP	
Sequence	Not applicable
Dose Selection: 0.04 U/min is the routinely used infusion rate for AVP in the tertiary medical center	
Investigational Drugs and Formulations: Identity and manufacturer of AVP not indicated. Publication does not state that vasopressin was dissolved in isosaline for infusion.	
Administration: Intravenous constant rate infusion of 0.04 U/min AVP	
Inclusion Criteria: Septic shock was defined as hemodynamic instability with proven or suspected infection and one of the following non-respiratory systemic inflammatory response syndrome criteria: body temperature > 38 C or < 36 C, heart rate > 90 bpm, or a white blood cell count > 12000/mm^3 or < 4000/mm^3 or presence of >10% immature forms. Hemodynamic instability was defined as MAP ≤70 mm Hg and a systolic blood pressure (SBP) ≤ 90 mm Hg. Patients were required to have a positive fluid balance in the 24 h before start of the AVP. Infection or suspected infection was defined as positive growth on cultures of samples obtained from sterile sites or blood, as well as the use of broad-spectrum antibiotics within 3 days before beginning AVP infusion.	
Exclusion Criteria: All patients not fulfilling inclusion criteria, patients receiving AVP for the treatment of variceal bleeding, hepato-renal syndrome or other non-septic and vasodilatory shock states and patients receiving AVP infusions for < 1 h were excluded.	
Fed/Fasted: Not indicated	
Interfering Substances: beta-blockers, amiodarone, drotrecogin alfa, opioids, sedatives, paralytics, insulin and parenteral nutrition could have potentially impacted the effect of vasopressin.	
PK Sampling Times: Blood samples for the determination of AVP were not collected	
PD Sampling Times: Baseline, 1 and 6 h after AVP infusion start	
Analytical Method: Not applicable	
Target PK Parameters: Not applicable	
PK Data Analysis: Not applicable	
Target PD Parameters: Blood pressure and heart rate (HR) at baseline, 6 and 24 h after initiation of the AVP infusion. Central venous pressure at baseline was also available. Baseline values were data collected within 24 h before initiation of the infusion of AVP.	
Data Analysis: Patients were assigned to pre-determined groups defined by body mass index (BMI) as follows: < 25 kg/m^2 (Group 1), 25-29.9 kg/m^2 (Group 2), 30-34.9 kg/m^2 (Group 3) or ≥ 35 kg/m^2 (Group 4). Pertinent laboratory parameters, hemodynamic measurements, and organ function were used to calculate Acute Physiology and chronic Health Evaluation II (APACHE II), Simplified acute Physiology II (SAPS II), and Sequential Organ Failure Assessment (SOFA) scores. Laboratory data renal, hepatic, cardiac enzyme, electrolyte, blood gas, glucose, and endocrine tests (Corticotropin stimulation test (if possible).	
Statistical Method: Analysis of variance was used when a continuous variable was compared among the four groups. The Pearson $\chi 2$ test was used for binary outcomes. Differences in reaching hemodynamic stability were assessed by using multiple logistic regression models in which BMI was considered a necessity risk factor. Other variables	

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assessed were SOFA and APACHE II scores, age, sex, use of a β-blocker on the day of AVP infusion and use of a corticosteroid during treatment with AVP. A step-wise elimination strategy was applied with all the variables. All tests were two tailed.
Sample Size/Power: The goal of the study is to provide preliminary information. Therefore the selected sample size is not based on power considerations.

Results

Study Population:

Of 618 patients identified receiving an AVP infusion, 66 were included in the analysis. Excluded were 302 not mechanically ventilated patients, 178 patients not meeting the septic shock criteria, 63 patients who did not receive an AVP infusion as the initial pressor agent and 9 patients received AVP by a titration regimen. The selected patients fit in the 4 groups as follows: 12 in Group 1, 22 in Group 2, 13 in Group 3 and 19 in Group 4.

The below tables list the baseline characteristics of the patients:

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Except for the central venous pressure (and BMI and body weight) the baseline characteristics were similar in the 4 groups. Except for overall use of corticosteroids no major differences in baseline concomitant drugs existed among the 4 groups.

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Overall 80% and 83% of patients had an MAP ≥ 65 mm Hg at 1 and 6 h, respectively., after initiation of the vasopressin infusion as shown in the below figure:

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There was no significant difference among the 4 groups in attaining the MAP goal.

Baseline mean MAP was 61 (8.5) mm Hg. The mean change from baseline at 1 and 6 h was 14 and 15 mm Hg, respectively, a shown in the below figure:

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At no time point was there a difference in MAP from baseline among the 4 groups. None of the evaluted variables was independently associated with attaining hemodynamic

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stability with an infusion of AVP as shown by the results of the below table:

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The mean duration of the AVP infusion was 1.9 days with no significant difference among the 4 groups.

The results on the secondary outcomes measures are shown in the below table:

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After the initial 6 h 14 patients required rescue catecholamine therapy. The mean length of stay in the ICU and the hospital was 16 (15) days and 43 (38) days, respectively. The mortality rate at the time of ICU and hospital discharge was 21% and 38%, The ICU mortality rates among the patients varied significantly among the groups whereas 28 mortality and hospital mortality were not different among the groups.

Serum creatinine decreased from baseline by 0.13 mg/dL with no significant difference among groups as shown in the below figure:

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Safety

- Was there any death or serious adverse events? ☑Yes ☐ No ☐ NA

Conclusion

- Constant rate infusion of AVP 0.067/min raises MAP by 14-15 mm Hg relative to baseline.
- Body mass index is not impacting the hemodynamic response to AVP
- Limitations: Retrospective design. Possible selection bias favoring AVP alone therapy in patients with less severe forms of sepsis. In addition, bias in judging need for rescue therapy. Inadequate fluid resuscitation could have confounded blood pressure response.

Comments

- None

6.5

Report #	**Study Period:** August 5, 1997-March 21, 1999	**EDR Link:**
Title	The Effect of Vasopressin on Hemodynamics and Renal Function in Severe Septic Shock: A Case Series. Holmes CT, Walley KR, Chittok DR, Lehman T, Russel JA. Intensive Care Med 2001; 27:1416-1421	
Study Design: Retrospective case series study of patients admitted to a 14 bed mixed medical surgical ICU of a 450 bed tertiary referral hospital (St. Paul Hospital in Vancouver) affiliated with the University of British Columbia. All patients receiving vasopressin treatment of severe septic shock during the periods of August 5, 1997, and		

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March 21, 1999, were included in the study. In general vasopressin was given to patients who were not responding to adequately to moderate or high doses of norepinephrine.

Rationale: Because of the published results of previous studies vasopressin (AVP) has been used in the critical care unit of St. Paul's Hospital since 1997 as a rescue therapy for patients with severe septic shock. What is not known about vasopressin from the literature is whether vasopressin is titratable and safe.

Objectives: Primary: To collect information on whether AVP is titratable and explore the adverse events associated with the treatment and its safety.

Screening: Not applicable	**Washout:** Not applicable
Periods	Not applicable

Treatment: Intravenous infusion of AVP

Sequence	Not applicable

Dose Selection: 0.01-0.06 U/min

Investigational Drugs and Formulations: Source and identity of the vasopressin infused are not provided. Publication does not state that vasopressin was dissolved in isosaline for infusion.

Administration: Intravenous infusion

Inclusion Criteria: All patients were included in the study who met two out of four criteria for systemic inflammatory response syndrome (SIRS) with a documented source of infection and who received vasopressin for a minimum of 2 h. SIRS is defined in the below table:

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Exclusion Criteria: Patients receiving vasopressin for control of gastrointestinal bleeding or for vasodilatory shock resulting from open-heart surgery.

Endpoints: Mean arterial Blood pressure (MAP), systemic pulmonary arterial pressure (SAP), cardiac index (CI), urine output and pressor dose. In addition, the charts were examined to determine potentially serious adverse consequences of AVP infusion such as ventricular arrhythmias, myocardial infarction or cardiac arrest and cause of death.

Fed/Fasted: Not indicated

Interfering Substances: Not indicated

PK Sampling Times: No blood samples collected for the determination of AVP

PD Sampling Times: Baseline, 4, 24 and 48 h after start of AVP infusion

Analytical Method: Not indicated

Database: Age, sex, APACHE II score 24 h prior to starting vasopressin, source of sepsis and hospital mortality. Only for patients receiving vasopressin for ≥ 4 h, additionally information on hemodyamic data (mean arterial blood pressure (MAP), systolic pulmonary arterial blood pressure (SAP), cardiac index (CI), urine output/h, dose of vasopressin/h and dosage of other vasoactive agents, i.e. total units of dopamine (µg●kg●min+3) plus

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norepinephrine μg/min plus epinephrine μg/min. The rationale and source for using this formula was not provided by the publication. The units for dopamine, epinephrine and epinephrine and the weighting of 3 pressor agents is different.

Statistical Method/Sample Size/Power: Repeated measures analysis was used to test for differences in continuous variables at baseline, 4, 24 and 48 h of infusion of vasopressin. Univariate F-tests were used to find the difference in the variables at each time point.

Results

Ninety-one (91) patients were identified who received vasopressin in the ICU during the critical time period. Fifty (50) patients received vasopressin for ≥ 2 h for septic shock. Five (5) of the 50 patients received vasopressin for < 4 h and therefore hemodynamic variables were no recorded in these 5 subjects. The demographic and clinical characteristics of the patients are shown in the below table:

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The patients were severely ill as evidenced by the high APACHE II score and there was a high prevalence of underlying co-morbid disease. The average dose of vasopressin was 0.05 U/min (range 0.01-0.06 U/min). Hospital mortality was 85%.

The impact of the vasopressin infusions on the primary endpoints are shown in the below figure:

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Relative to baseline MAP increased significantly by 18% at 4 h and remained at that level 24 and 48 h later. SAP remained unchanged at 45(13) mm Hg and CI decreased by 11% relative to baseline at 4 hand did not changed past that time point. Urine output (excluding anuric patients) at 4 h increased significantly 79% relative to baseline and further increases were not significant. Mean pressor dosage decreased significantly by 33% at 4 h, decreased further by 53% at 24 h and 48% at 48 h.

The degree of improvement in MAP, pressor dosage and urine output was not related to the rate of AVP infusion. However, infusion rates < 0.03 U/min were significantly correlated with a decrease in CI.

Eight (8) patients survived to hospital discharge. The cause of death in the remaining 42 patients were refractory shock (n=20), withdrawal of care due to multiple system organ failure (n=19), respiratory failure later on the ward (n=2) and cerebral edema due to

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underlying disease (n=1). There were 6 cardiac arrests. All of these patients were in severe refractory shock.
Safety
▪ Was there any death or serious adverse events? ☑Yes ☐ No ☐ NA
Conclusion
• Infusions of vasopressin increased MAP by 18% relative to baseline. SAP remained unchanged and CI decreased by 11% relative to baseline at 4 h and did not change past that time point. • There was a transient 79% increase in urine output at 4 h relative to baseline. • Mean pressor dosage decreased significantly by between 33% and 53% during the infusion with vasopressin. • The changes in MAP, pressor dosage or urine output were not related to the rate of vasopressin infusion. However, infusion rates < 0.03 U/min were significantly correlated with a decrease in CI. • Eight (8) patients survived to hospital discharge. Limitations: • The study has a retrospective design • Absence of control for progression of underlying disease or co-interventions such as fluid therapy and corticosteroid use .Both could alter outcome variables. • Timing of the entry in the study was not controlled. As a consequence the duration of the septic shock varied among the patients. • Patients did not receive vasopressin in accordance with strict guidelines • Rationale and source for formula used to compute the pressor dosage is not provided
Comments
• None

6.6

Report #	**Study Period:** Not indicated	**EDR Link**
Title	Vasopressin Deficiency Contributes to the Vasodilation of Septic Shock. Landry DW, Levin HR, Gallant EM, Ashton RC, Seo S, D'Allessandro D, Oz MC, Oliver JA. Circulation 1997;95: 1122-1125	
Study Design: 31 consecutive adult subjects with vasodilatory shock meeting the entry criteria of vasodilatory septic shock or cardiogenic shock admitted to the intensive care units of 2 hospitals and meeting the inclusion criteria were enrolled. The plasma levels of endogenous vasopressin (AVP) were measured in all patients. Exogenous AVP was administered by intravenous infusion at a constant rate of 0.04 U/min. In 2 patients the plasma levels of exogenous AVP were measured after administration of an infusion with a		

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rate of 0.01 U/min. Six (6) patients receiving vasopressin (0.01 U/min) as sole pressor were subsequently weaned from vasopressin for a period and then the vasopressin infusion at the same rate was resumed. Hemodynamic and clinical endpoints were measured before and after administration of exogenous AVP. Continuous measurements of systolic arterial blood pressure (SAP) and heart rate (HR) were averaged in 15 min intervals. Intravenous fluids and medications were not changed for the hour before of the first hour of vasopressin administration except that during vasopressin administration pressor catecholamines (norepinephrine (NE), epinephrine, dopamine, neosynephrine) were decreased if the systolic arterial blood pressure (SAP) exceeded 130 mmHg.
Rationale: Vasopressin does not play a major role in the control of vascular smooth muscle in normal conditions, but becomes critical when maintenance of an adequate blood pressure is threatened. Some patients with advanced vasodilatory shock appear to be very sensitive to the pressor effects of exogenous vasopressin. This observation suggests that endogenous vasopressin may be inappropriately low in this population. Thus, the hypothesis was examined that vasopressin deficiency could contribute to the vasodilation of septic shock.
Objectives: Primary: To measure endogenous vasopressin levels in patients with vasodilatory shock and to measure the plasma levels of exogenous AVP in a subgroup of the patients before administration of catecholamines,
Endpoints: SBP, DSP, cardiac output, SVR, HR Catecholamine dose requirements
Inclusion Criteria: Septic shock was defined by systolic blood pressure (SBP) ≤ 90 mm Hg (in the absence of antihypertensive agents) and low vascular resistance (<800 dyne x s/cm^3), fever (>101° C) or hypothermia (< 97° C), tachypnoa (respiratory rate > 90 bpm or mechanical ventilation and either positive blood culture r obvious source of infection (WBC >12000 mm^3 or < 4000 mm^3 or > 10% immature band forms) and elevate prothrombin or partial thromboplastin time or reduction of platelet count or <100000/mm^3). In all septic patients , hypotension persisted after fluid administration (PAOP >12 mm Hg) and require administration of catecholamines (NE, epinephrine, dopamine and/or neosynephrine to maintain SBP > 90 mm Hg for 1 or 2 days. Cardiogenic shock was defined as SBP ≤ 90 mm Hg, PAOP > 15 mm Hg and CI ≤ 2.5 L/min before catecholamine. Patients with fever, hypothermia, or an obvious source of infection were not included in the group of patients with cardiogenic shock.
Exclusion Criteria: < 18 y of age, suspected pregnancy, presence of coronary artery disease or mesenteric ischemia.
Screening: Not indicated | **Washout:** Not applicable
Periods | Not applicable
Treatment: AVP 0.04 U/min by constant intravenous infusion
Sequence | NA
Dose Selection: Infusion rates of 0.245 U/min have been tolerated by healthy subjects
Investigational Drugs and Formulations: Vasopressin® (vasopressin Injection USP, 8 arginine vasopressin). The publication does not state that AVP was dissolved in isosaline for infusion.
Administration: Constant rate infusion of 0.04 U/min AVP into central vein
Fed/Fasted: Not indicated
Interfering Substances: Not indicated

Reference ID: 3313815

PK Sampling Times: Before and after initiation of infusion of exogenous AVP at steady-state (time not indicated)

PD Sampling Times: Before and after initiation of infusion of exogenous AVP (first hour average values from the 15 min interval in which SAP reached a maximum)

Analytical Method

Analyte		AVP
Method		RIA
Matrix		Plasma
Range, pg/mL		0.8-8.0
Quality Control	%CV	Not indicated
	%RE	Not indicated

After mixing with 0.1 n HCL 0.5 mL plasma was passed through a SEP-PAK C18 cartridge and extracted with methanol. The recovery of the extraction procedure was 95%. Standard curves ranging from 0.5 to 8.0 pg/mL were established. Known concentrations of AVP added to plasma showed a mean recovery of 87%. The intra- and inter-assay coefficients of variations for 3 pooled plasma samples ranged between 7.9-14% and 8.2 and 14%, respectively. The minimum detection limit was 0.05 pg/tube. The assay is equally sensitive to AVP and lysine vasopressin. However cross-reactivity towards oxytocin, DDAVP, vasotocin and pressinoic acid is negligible. Plasma samples containing two different AVP concentrations were serially diluted 2 to 32 fold using 0.1 M phosphate buffer resulting in a proportional right shift of the corresponding curves. Sample stability was tested at -30 ˚C, 4 ˚C and room temperature for 1 month. At -30 ˚C AVP was stable. However, at 4 ˚C and at room temperature the AVP concentration was reduced by up to 32% and 45%, respectively, after 1 month.

Target PK Parameters: Steady-state plasma concentrations of endogenous and exogenous AVP.

PK Data Analysis: CL=Css/ko for exogenous AVP

Target PD Parameters: Systolic and diastolic arterial blood pressure (SAP, DAP))and other hemodynamic endpoints before and after infusion of AVP

Statistical Method/Sample Size/Power: The systolic blood pressure data during AVP infusion at a rate of 0.04 U/min, during AVP infusion stop and again after resuming the infusion of AVP at a rate of 0.01 U/min were analyzed by unpaired t-test. The data before and after administration of the AVP infusions were analyzed by paired t-test.

Results

Study Population:

Consecutive patients meeting entry criteria	31
Septic shock	19
Cardiogenic shock	12
Treated with exogenous AVP	
Septic shock	10
Cardiogenic shock	6
Completed study	31
Completed PK	16
Discontinued	0

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Pharmacokinetic population Endogenous AVP Exogenous AVP Safety population	 31 2 16 31
Age [Mean (SD)], years	Not indicated
Weight [Mean (SD)], kg	Not indicated
Male/Female	Not indicated
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated

The 19 subjects with septic shock displayed severe hypotension requiring administration of catecholamines. Despite catecholamine administration, the hemodynamic data of the patients with septic shock showed hypotension due to low systemic vascular resistance as shown in below table:

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PK

Endogenous AVP

The below figure shows the individual and mean (SEM) plasma concentrations of endogenous AVP prior to administration of exogenous AVP in the subjects with septic and cardiogenic shock:

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The mean (SEM) plasma levels of endogenous AVP in the subjects with septic shock of 3.3(0.4) pg/mL were significantly lower than the levels in the patients with cardiogenic shock of 22.7 (2.2) pg/mL, respectively. Only one of the subjects with cardiogenic shock displayed an endogenous AVP value in the range of the patients with septic shock.
The plasma concentrations of exogenous AVP attained during an infusion of 0.01 U (18.5 ng/min) in 2 patients with septic shock were 27 and 34 pg/mL. The respective clearances calculated from CL=ko/Css were 685 and 544 mL/min for the 2 patients with septic shock.

PD

Exogenous AVP

The below table shows the mean(SEM) hemodynamic values and the ranges of the catecholamine infusion rates in 10 patients with spetic shock before and after infusion of exogenous AVP:

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AVP on average increased SAP and DBP by 52 mm Hg and 14 mm Hg relative to base line. This is due to an increase in systemic vascular resistance. AVP decreases CO and does not impact HR.

The below figure depicts the response of SAP in 6 subjects with septic chock to the administration of a constant intravenous infusion of 0.01U/min AVP, withdrawal of the AVP infusion and re-administration of the AVP infusion at the same rate of 0.01U/min:
:

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The 6 patients received only AVP as vasopressor. The results show the reproducible pressor effect of AVP in the subjects with septic shock on AVP, after withdrawal of AVP and following resumption of the infusion.

Safety

- Was there any death or serious adverse events? ☐ Yes ☐ No ☑ NA

Conclusion

- The mean (plasma levels of endogenous AVP in subjects with septic shock [3.3(0.4) pg/mL] are significantly lower than the levels in patients with cardiogenic shock [22.7 (2.2) pg/mL], respectively.
- Relative to baseline, exogenous AVP increases SAP, DAP, and systemic vascular resistance, decreases CO and does not impact HR.
- The pressor effect of exogenous vasopressin in subjects with septic shock fades after infusion stop and reappears when the infusion is resumed.

Reference ID: 3313815

Comments
• Relevant demographic data (for example age, sex , weight) of the patients investigated are not reported
Reference 1. Sakurai, KA, Kurimoto F, Ohono H, Kanai A, Nomura K, Demura H, Shizume K. Folia Endocrinol 1985; 61: 724-736

6.7

Report #	**Study Period** : Not stated	**EDR Link**
Title	Beneficial Effect of Short-Term Vasopressin Infusion during Severe Septic Shock. Patel BM, Chittock DR, Russell JA, Walley KR. Anesthesiology 2002; 96:576-582	
Study Design: Double-blind, randomized, active controlled study. Either vasopressin or norepinephrine (NE) was infused for 4 h in patients with severe septic shock who required high-dose vasopressors despite adequate fluid resuscitation. The study was conducted in 2 centers. The study drug was titrated to maintain mean arterial blood pressure (MAP) while cardiac index (CI) and surrogate markers for specific organ perfusion, including urine output and creatinine clearance, gastric-arterial carbon dioxide tension (pO2) gradient and ST-segment changes were measured. Twenty-four (24) patients were enrolled. The etiology of septic shock was documented infection in 22 patients. The starting infusion rate for AVP was 0.01U/min or NE 2 µg/min. The maximum infusion rate for vasopressin was 0.08 U/min and for NE 16 µg/min. During the initial 60 min of the 4 h infusion the study drugs were titrated to every 5-10 min and the pre-study vasopressor (in all cases NE) was titrated down to maintain MAP constant at a level determined by the attending intensive care physician. All other medications were held constant, dobutamin infusion was not adjusted and mechanical ventilator setting remained unchanged. No patient deteriorated during the 4 h infusion period. At baseline and at the end of the 4 h infusion the endpoints were measured		
Rationale: to test the hypothesis that vasopressin has a vasopressor sparing effect while maintaining hemodynamic stability and end-organ perfusion.		
Objectives: Primary: To compare the short term physiologic effects of vasopressin vs. norepinephrine patients with hyperdynamic septic shock requiring high dose vasopressors.		
Screening: not applicable		**Washout: Not applicable**
Periods	Not applicable	
Treatment: Vasopressin infused at a median rate of 0.06 U/min. The infusion rate of NE in the vasopressin group was reduced from initially 25 to 5.3 µg/min. In the group randomized to the NE the baseline infusion rate was 20 µg/min and after 4 h was 17 µg/min.		
Sequence	NA	
Dose Selection: Infusion rates in the range of 0.01-0.08 for vasopressin and 2-16 µg/min have been used in other studies.		
Investigational Drugs and Formulations: Not stated		
Administration: Intravenous		

Reference ID: 3313815

Inclusion Criteria: Patients with hyper-dynamic severe septic shock and end-organ dysfunction unrelated to the primary sepsis focus, were adequately volume resuscitated (500 mL crystalloid bolus or 250 mL 5% albumin and pulmonary wedge pressure >12 mm Hg) were on high dose vasopressors and had a pulmonary artery catheter in place and had a CI > 2.0L/m2. Sepsis was defined using standard criteria as shown in the below table: COPYRIGHT MATERIAL High dose vasopressor support was defined as follows: [NE dose (µg/min) + epinephrine dose (µg/min) + dopamine dose/4 (µg/min) > 5 for > 1 h. these criteria fulfill the definition of septic shock and approximately correspond to severe cardiovascular failure as defined by the Sequential Organ Failure Assessment score.
Exclusion Criteria: Pregnancy, hypersentivity to study drugs, had acute coronary artery disease present or suspected, severe hyponatremia (serum sodium < 125 mEq/L) not responding to water restriction, or Raynaud syndrome, systemic sclerosis, or vasospastic diathesis.
Endpoints: Primary: NE dose requirements, Secondary: Hear rate (HR), pulmonary artery pressure PMAP, pulmonary artery occlusion pressure (PAOP), cardiac index (CI) (by thermodilution), systemic vascular resistance (SVR) was calculated from the MAP- right atrial pressure divided by CI. Pulmonary artery vascular resistance was calculated as the mean pulmonary artery pressure minus pulmonary artery occlusion pressure divided by CI. Gastric mucosal PCO2 was measured by a nasogastric tonometer. Urine output was averaged over 4 h before the study and the repeat measure was averaged over 4 h during study drug infusion. Simultaneously in blood and in a 4 h urine collection creatinine, sodium and osmolality at baseline and after 4 h study drug infusion was measured.
Fed/Fasted: Not stated
Interfering Substances: Not stated
PK Sampling Times: Prior to and 4 h after start of the infusions of study drug
PD Sampling Times: at baseline and after 4 h of infusion with study drug
Analytical Method Vasopressin was measured by RIA. No information on the validation or performance of the RIA was provided.
Target PK Parameters: Plasma concentrations of vasopressin 4 h after initiation of infusion.
PK Data Analysis: None
Target PD Parameters: MAP, CI, PVR, pulmonary artery wedge pressure, pulmonary artery pressure
Statistical Method: Sample Size/Power: Non-parametric statistical methods were used. The Mann-Whitney test was used to for continuous variables and the chi-square test for proportions. Changes

Reference ID: 3313815

form baseline to 4 h in outcome variables between the two study groups using a Kruskal-Wallis analysis of variance. All data are reported as median with 25th and 75th percentiles. The goal of the study is to provide preliminary information. Therefore the selected sample size is not based on power considerations.

Results

Study Population:

The baseline characteristics of the patients randomized to receive the vasopressin and NE treatments are shown in the below table and show that the 2 groups were adequately matched. :

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PD

The results on the hemodynamic variables are shown in the below table:

Table 3. Hemodynamic Variables

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After 4 h infusion of vasopressin MAP remains the same, HR decreases by 9 bpm and the CI by 0.4 L/m2 and PVR and PAOP tend to increase. After 4 h infusion of NE MAP is reduced by 1 mm Hg, HR decreases by 5 bpm and CI by 1 L/m2. PAOP and SVR tend to increase slightly.

A significant decrease in the dose requirements for NE in the presence of AVP is noted as shown in the below figure:

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The NE dose requirements in the vasopressin group decreased by 79% and in the NE group by 15%. Urine output and creatinine clearance in the vasopressin group were also statistically significantly increased after 4 h of infusion whereas urine output in the NE group tended to be reduced.

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Vasopressin also increased creatinine clearance. There were no changes in osmolality or serum sodium in plasma or urine in the vasopressin group. Vasopressin did not alter PCO_2 suggesting no important change in the gastric blood supply. No changes in ST segment in the ECG occurred.

PK

The plasma concentrations of vasopressin at baseline were similar I both groups (1.3 (0.9) pg/mL after infusion of vasopressin the concentrations increased to 17.1 (3.9) pg/mL.

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Safety
▪ Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
Conclusion
• A 4 h infusion of median 0.060 U/min vasopressin in the presence of NE infused at 5.3 µg/min to patients with NE refractory hyperdynamic severe septic shock does not increase MAP in patients with baseline MAP of 68 mm Hg. NE infused at a median rate of 17 µg/min results in a reduction of MAP of 1 mm Hg relative to baseline. • The reduction dose requirements of NE in the presence of vasopressin is significant • Vasopressin increases urine output and creatinine clearance significantly • Gastric tonometry did not show evidence for an overt gastric ischemia • No effect of vasopressin on osmolality or sodium in plasma or urine was observed.
Comments
No comments

6.8

Report #	**Study Period:** Not indicated	**EDR Link**
Title	High-Dose Vasopressin is not Superior to Norepinephrine in Septic Shock. Klinzing S, Simon M, Reinhart K, Bredle DL, Meier-Hartman A. Crit Care Med 2003;31:2646-2650	
Study Design: Consecutive series design study in 12 mechanically ventilated patients with septic shock with consecutive administrations of norepinephrine (NE), NE + vasopressin (AVP), and NE. Before data collection the patients were stabilized by volume loading until there was no further increase in cardiac output. The patients required 0.18-1.10 µg/kg/min NE to maintain a mean arterial blood pressure (MAP) of 70 mm Hg. All patients were treated with dobutamine (2.0-4.5 µg/kg/min). The infusion rate of dobutamine was kept constant during the experiment. Once the hemodynamics and blood gas values stabilized in the patients on NE three consecutive measurements of the target endpoints were made. Thereafter the infusion of vasopressin was started until the NE infusion could be entirely stopped without reducing MAP < 70 mm Hg. After 2 h of stabilization three consecutive measurements were carried out. In the next phase the vasopressin infusion was stopped and the NE infusion restarted as appropriate. Urine output was monitored hourly throughout the study.		
Rationale: The hepato-splanchnic perfusion is critically involved in the etiology of septic shock via loss of mucosal barrier function and consequent bacterial translocation. There is no consensus on which vasopressor, dopamine, norepinephrine (NE) or vasopressin to use		

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in septic shock. There is a lack of comparative data for NE and vasopressin.		
Objectives: Primary: To determine the comparative vasoconstriction of NE and vasopressin		
Endpoints: Mean arterial blood pressure (MAP), cardiac index (CI), heart rate (HR), central venous pressure (CVP), hepatosplanchnic blood flow, gastric mucosal pCO_2 gap, global O_2 delivery, global O_2 consumption, splanchnic O_2 delivery, splanchnic O_2 consumption, O_2 saturation in hepatic vein, PCO_2 gap, arterial lactate concentration		
Inclusion Criteria: Mechanically ventilated adult patients with septic shock. Septic shock was defined according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. The patients required 0.18-1.10 µg/kg/min NE to maintain MAP of 70 mmHg.		
Exclusion Criteria: Not indicated		
Screening: Not indicated		**Washout:** None
Periods	3	
Treatments: NE followed by vasopressin followed by NE		
Sequence	NE → NE + AVP→NE	
Dose Selection: NE: 0.18-1.10 µg/kg/min, AVP: 0.06-1.8 U/min		
Investigational Drugs and Formulations: Source of NE and source and type of AVP were not identified by the publication. The publication does not indicate that AVP was dissolved in isosaline for infusion		
Administration: Intravenous infusion		
Fed/Fasted: Enteral nutrition was stopped ≥ 2 h before study start		
Interfering Substances: Co-administered drugs included fentanyl and midazolam or sulfentanil and propofol for sedation, and ranitidine		
PK Sampling Times: No blood samples for the determination of NE or AVP were collected		
PD Sampling Times: At baseline, during NE infusion, during AVP infusion after removal of NE infusion, after replacing AVP infusion by NE infusion		
Analytical Method Hepato-splanchnic blood flow was determined using a bolus followed by a constant infusion of indocyanine green. Indocyanine green was measured by spectrophotometry. Gastric mucosal PCO_2 gap was determined by air tonometry. PCO_2 gap was calculated as the difference between gastric regional CO_2 tension and CO_2 tension in the corresponding arterial blood sample.		
Target PK Parameters: Not applicable		
PK Data Analysis: Not applicable		
Target PD Parameters: CI, HR, MAP, hepato-splanchnic blood flow, gastric mucosal pCO_2 gap, global O_2 delivery, global O_2 consumption, splanchnic O_2 delivery, splanchnic O_2 consumption, O_2 saturation in hepatic vein, PCO_2 gap, arterial lactate concentration		
Statistical Method/Sample Size/Power: Paired data obtained before and after conversion to AVP were compared with a non-parametric Wilcoxon rank-sign test. The selected sample size was not based on power considerations.		
Results		

Reference ID: 3313815

Study Population:

Treated Completed Discontinued Pharmacodynamic population Safety population	12 12 0 12 12
Age [Median (range)], years	67 (28-75
Weight [Mean (SD)], kg	Not indicated
Male/Female	7/5
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated

The patients' characteristic are shown in the below table:

The Acute Physiology and Chronic Health Evaluation (APACHE) score of the patients raged between 19 and 38.

PD

Replacement of NE (0.56 µg/kg/min) by vasopressin (0.47 U/min) was associated with a significant reduction in HR and CI as shown in the below table:

Variable	During NE Infusion	During Vasopressin Infusion
CI, L/min/m2	3.8 (1.3)	3.0 (1.1)*
HR, bpm	96 (14)	80 (16)*
Global O_2 Delivery, mL/min	891(349)	643 (272)*
Global O_2 Uptake, mL/min	248 (67)	218 (75)*
Hepato-splanchnic Blood Flow, mL/min	0.8 (0.5)	1.2 (1.1)
Percent Hepatoc-splanchnic Blood Flow, %	10.8(7.6)	25.9 (16.6)*
Splanchnic O_2 Delivery, mL/min	101(64)	131 (109)
Splanchnic O_2 Consumption, mL/min	51 (40)	79 (65)
O_2 Saturation in Hepatic Vein, %	46.6 (16.2)	36.1 (16.7)
PCO_2 gap, mm Hg	17.5(26.6)	36.5 (26.6)*,[a]
Arterial Lactate, meq/L	2.3(0.8)	2.8 (1.5)

*Statistically significant [a]Results on the PO_2 gap were not available for 2 of the 12 patients because of technical problems

Replacing NE by vasopressin resulted in significant reductions of HR, CO, global O_2 consumption and gastric regional PCO_2 gap. Splanchnic blood flow tended to increase with vasopressin, but the change was not significant. The hepatosplanchnic blood flow in % of the cardiac index increased with vasopressin significantly, which mitigated the reduction in O_2 delivery partially.

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- No death occurred during the study period. However, 7 of the 12 patients died after study completion.

Conclusion

Reference ID: 3313815

• At infusion rates in the range between 0.06 and 1.8 U/min vasopressin increased the pCO_2 gap significantly compared to NE infused at rates between 0.18 and 1.1 µg/kg/min. Replacing NE by high doses of AVP may not be beneficial.
Comments
• None

7. PD in Adult Patients with Target Disease: Post-Cardiotomy Shock

7.1

Report #	**Study Period**	**EDR Link**
Title	A Prospective, Randomized Trial of Arginine Vasopressin in the Treatment of Vasodilatory Shock after Ventricular Assist Device (LVAD) Placement. Argenziano M, Choudhri AF, Oz MC, Rose EA, Smith CR, Landry DW. Circulation.1997; 96:II-286-II290	
Study Design: Randomized, double-blind, placebo controlled. Patients undergoing standard cardiac anesthesia protocol for Cardiopulmonary Bypass (CPB) and weaned from CPB were selected for 1) mean arterial pressure (MAP) ≤ 70 mmHg despite norepinephrine (NE) of > 8 µg/min 2) LVAD assisted cardiac index (CI) >2.5 L/min/m^2. Consecutive eligible patients blindly randomized 5 min after CPB to receive intravenous vasopressin (Pitressin® Parke-Davis) at 0.1 U/min or normal saline. A plasma sample for vasopressin measurement was collected at the time of randomization. A clinical response was defined as an increase in MAP > 20 mm Hg without an increase in NE administration and/or increase in NE requirements (> 5 µg/min) without a decline in MAP, in the absence of other pharmacologic or surgical interventions. In the absence of a clinical response after 15 min of infusion, the patients were eligible at the discretion of the attending surgeon for blinded administration of the alternative solution. If a clinical response was observed, the assigned infusion was continued post-operatively. On arrival in the ICU the AVP infusions were decreased to maintain MAP > 70 mm Hg without catecholamine support.		
Rationale: Vasodilatory shock can occur after CPB as part of a systemic inflammatory response. Catecholamines are used to treat this syndrome, but catecholamine resistance is common and significant toxicity can occur at high doses.		
Objectives: Primary: To determine the value of vasopressin in post-CPB vasodilatory shock		
Endpoints: MAP, systemic vascular resistance (SVR), NE requirements, mean pulmonary arterial pressure (MPAP)		
Inclusion Criteria: Decreased MAP (≤70 mm Hg), increased CI (> 2.5 L/min/m^2) and NE infusion rate > 8 µg/min		
Exclusion Criteria: Not stated		
Screening: not indicated	**Washout:** Not applicable	
Periods	Not applicable	
Treatment: AVP and normal saline		

Reference ID: 3313815

Sequence	Not applicable

Dose Selection: AVP infusion rate of 0.1U/min has been used safely previously in patients with vasodilatory shock

Investigational Drugs and Formulations: AVP Pitressin® (Parke-Davis). The publication does not state that AVP was dissolved in isosaline for infusion

Administration: Intravenous infusion

Fed/Fasted: Fasted

Interfering Substances: Not stated

PK Sampling Times: At time of randomization

PD Sampling Times: 5 min after completion of CPB and 15 min into the infusions

Analytical Method

Analyte		AVP
Method		RIA
Matrix		Plasma
Range, pg/mL		0.8-8.0
Quality Control	%CV	Not indicated
	%RE	Not indicated

After mixing with 0.1 n HCL 0.5 mL plasma was passed through a SEP-PAK C18 cartridge and extracted with methanol. The recovery of the extraction procedure was 95%. Standard curves ranging from 0.5 to 8.0 pg/mL AVP were established. Known concentrations of AVP added to plasma showed a mean recovery of 87%. The intra- and inter-assay coefficients of variations for 3 pooled plasma samples ranged between 7.9-14% and 8.2 and 14%, respectively. The minimum detection limit was 0.05 pg/tube. The assay is equally sensitive to AVP and lysine vasopressin. However cross reactivity towards oxytocin, DDAVP, vasotocin and pressinoic acid is negligible. Plasma samples containing two different AVP concentrations were serially diluted 2 to 32 fold using 0.1 M phosphate buffer resulting in a proportional right shift of the corresponding curves. Sample stability was tested at -30 ˚C, 4 ˚C and room temperature for 1 month. At -30 ˚C AVP was stable. However, at 4 ˚C and at room temperature the AVP concentration was reduced by up to 32% and 45%, respectively, after 1 month.

Target PK Parameters: Post CPB plasma levels of endogenous AVP

PK Data Analysis: Not applicable

Target PD Parameters: MAP, CI, SVR

Statistical Method/Sample Size/Power: Paired variables were analyzed by the paired Student's t-test, and unpaired variables compared by the Wilcoxon non-parametric test. The selected sample size was not based on power considerations.

Results

Reference ID: 3313815

Study Population:

Ten (10) of 23 LVAD recipients met the inclusion criteria. Seven subjects presented with ischemic cardiomyopathy and three with idiopathic dilated cardiomyopathy. These patients did not significantly differ from the 13 patients not meeting the criteria for vasodilatory shock relative to etiology of heart failure, ejection fraction, preoperative medication regimens, CPB time, or other basic demographic data. Their mean (SEM) MAP, CI and SVR were 60 (2) mmHg, 2.0 (0.1) L/min/m^2, 828 (70) dyne•s/cm^5 despite an NE infusion rate of 19.7 (5.4) µg/min indicating that they were in vasodilatory shock.

Treatments and demographics of the randomized patients are shown in the below table:

Randomized	10
AVP	5
Treated	5
Completed	5
Discontinued	0
Saline*	5
Treated	5
Completed	5
Discontinued	0
Pharmacodynamic and –kinetic population	10
Safety population	10
Age [Mean (SD)], years	52
Weight [Mean (SD)], kg	Not indicated
Male/Female	8/2
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated

* 3 patients receiving the saline treatment were crossed over to vasopressin

PD

The impact of the 15 min infusions of vasopressin and saline on mean (SEM) MAP, CI, PVR and NE requirements are shown in the below table:

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The individual results for MAP, SVR and NE requirements in the patients receiving the AVP infusion are shown in the below table:

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The infusion with AVP increased MAP significantly by 26 mm Hg and SVR without changing CI relative to baseline suggesting that AVP's effect was mainly by vasoconstriction. The effects were seen consistently in all patients receiving AVP. The onset of the vasoconstrictor effect was seen within 15 min after initiation of the infusion. The requirements for NE decreased significantly as well. In 4 of the 5 subjects NE was discontinued within the 15 min time interval since start of the infusions. The fifth subject on AVP was slowly tapered off NE over several h despite a MAP of 90 mm Hg, at the discretion of the attending surgeon. The administration of AVP did not impact MPAP. The subjects receiving saline did not exhibit significant changes in MAP, SVR or NE requirement relative to baseline. In 3 patients who were blindly crossed over from saline to AVP, MAP and SVR increased and the NE requirement decreased clinically relevantly. Two of the patients were tapered off NE within 15 min after receiving vasopressin. The third patient was tapered off NE over several h after AVP initiation despite a MAP of 100 mm at the discretion of the attending surgeon.

For subjects maintaining a MAP of > 70 mm Hg without NE support AVP was tapered to 0.01 U/min and then discontinued. The median duration of AVP infusion was 36 h (1 h -7 days) and no patient required reinstitution of NE.

PK

The plasma concentration of endogenous AVP in the 10 patients measured prior to the initiation of exogenous AVP are shown in the below figure:

Reference ID: 3313815

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The AVP concentrations congregate in 2 clusters with means (SEM) of 8.8 (4.7) pg/mL and 33.7 (1.6) pg/mL.
Safety
▪ Was there any death or serious adverse events? ☑ Yes ☐No ☐ NA There was one perioperative death, occurring on postoperative Day 3, due to intractable hemorrhage in a patient with multisystem organ failure and severe coagulopathy.
Conclusion
▪ Constant infusion of 0.1 U/min AVP in patients after left ventricular assist device placement who developed vasodilatory shock raises clinically relevantly MAP and PVR relative to baseline without changing CI suggesting a vasoconstrictor effect of the drug. The dose requirements of NE are significantly lowered. ▪ The onset of the vasoconstrictor effect of AVP occurs within < 15 min. ▪ Post–cardiotomy endogenous AVP levels in the patients vary significantly
Comments
▪ None

7.2

Report #	**Study Period**	**EDR Link**
Title	Management of Vasodilatory Shock after Cardiac Surgery: Identification of Predisposing Factors and Use of a Novel Pressor Agent. Argenziano M, Chen JM, Choudhri AF, Collinane S, Garfein E, Weinberg AD, Smith CR, Jr, Rose EA, Landry DW, Oz MC. J Thorac Cardiovasc Surg 1998; 116:973-80	
Study Design: 145 patients undergoing cardiopulmonary bypass (CPB) were studied prospectively. Preoperative ejection fraction, medications and peri-operative hemodynamics were recorded and post-bypass serum levels of vasopressin (AVP) were		

Reference ID: 3313815

measured. The patients were selected on the basis of hypotension defined as mean arterial blood pressure (MAP) < 70 mm Hg during the first 30 min after CPB weaning and requiring norepinephrine (NE) for ≥ 3 h. Subjects were also classified as having cardiogenic shock (cardiac index (CI) < 2.5 L/min/m^2) or vasodilatory shock (CI>2.5 L/min/m^2). In the retrospective part of the study a review over a period of 30 months was performed to find cases of patients who received AVP. Fourteen (14) left ventricular device (LVAD) and 26 orthotopic heart transplant (OHT) recipients met theses criteria and received infusions of AVP at a rate of 0.1 U/min. Subsequently catecholamine agents and then AVP infusions were tapered to maintain MAP >70 mm Hg. When hemodynamic improvement allowed discontinuation, the AVP infusion rate was progressively decreased to 0.02 U/min and then discontinued.	
Objectives: Primary: To prospectively establish the incidence of vasodilatory shock in a general cardiac surgical population and the characteristics of this syndrome, including presence of AVP deficiency and other predisposing factors**. Secondary**: To retrospectively evaluate the own clinical experience with the use of AVP in the management of vasodilatory hypotension after CPB	
Endpoints: MAP, levels of endogenous AVP after CPB	
Inclusion Criteria: For prospective study**:** Vasodilatory shock was defined as MAP <70 mm Hg, CI >2.5 L/min/m^2 and NE dependence For retrospective study: Post-CPB vasodilatory hypotension (requirement of NE to maintain MAP > 70 mm Hg and CI > 2.5L/min/m^2.	
Exclusion Criteria: Not stated	
Screening: Not stated	**Washout:** Not applicable
Periods	Not applicable
Treatment: Constant intravenous infusion of AVP at a rate of 0.1 U/min	
Sequence	Not applicable
Dose Selection: 0.1 U/min AVP has been administered in previous studies without overt toxicity	
Investigational Drugs and Formulations: AVP (Pitressin, Parke-Davis, Morris Plains, NJ). The publication does not state that AVP was dissolved in isosaline for infusion.	
Administration: Intravenous	
Fed/Fasted: Not indicated	
Interfering Substances: Diuretics, ACE inhibitors, calcium channel blockers, bet-blockers, digoxin, preoperative routine medications	
PK Sampling Times: Post-cardiotomy	
PD Sampling Times: Prospective study: Prior to surgery and 30 min after weaning from CPB. **Retrospective study:** Peak effect measured within 2 h after initiation of the AVP infusions	
Analytical Method: Reference does not provide helpful information.	
Target PK Parameters: Post CPB plasma concentrations of endogenous AVP	
PK Data Analysis: Not applicable	
Target PD Parameters: MAP and relationship between baseline MAP and subsequent	

Reference ID: 3313815

increase during AVP infusion (retrospective study)

Statistical Method: Sample Size/Power: Continuous variables were analyzed with the paired and unpaired t-test and analysis of variance. The $\chi 2$ and Fisher exact tests were applied to discrete variables. Univariable and multivariable logistic regression analyses were used to determine the relative contribution of demographic and clinical factors to the development of vasodilatory hypotension. The goal of the study is to provide preliminary information. Therefore, the selected sample size is not based on power considerations.

Results

Prospective Study

The demographic of the 145 patients participating in the prospective study are listed in the below table:

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PK, PD

Eleven patients with vasodilatory and 9 patients with cardiogenic hypotension after CPB were identified. The patients with vasodilatory shock represented 8% of the total population investigated. The mean values for MAP, CI and endogenous AVP of the patients with shock are listed in the below table:

Reference ID: 3313815

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The below figure shows the individual endogenous AVP plasma concentrations of the patients with shock:

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The plasma concentrations of endogenous AVP were smaller in the patients with vasodilatory shock than those in cardiogenic shock suggestive of an AVP deficiency in vasodilatory shock.

Co-administration of ACE inhibitors and presence of low ejection fraction were identified as relevant risk factors for the development of post-CPB vasodilatory shock

Retrospective Study

The demographics of the 40 patients studied are listed in the below table:

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PD

The duration of the AVP infusion ranged between 1 h and 6 days.
The below figure shows the effect of the AVP infusions on MAP, SVR and NE dosage requirements:

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Of note the PD measurements were taken during the 0-2 h interval after initiation of the AVP infusions at a rate of 0.1 U/min when MAP reached a maximum. Relative to baseline MAP and SVR increased and the dose requirements for NE decreased in the patients with vasodilatory shock. CI did not change importantly. The MAP values after initiation of AVP were statistically significantly greater than the respective values at baseline. The percent increase of mean MAP above baseline in the patients with moderate (60-75 mm Hg), severe (50-59 mm Hg) and profound (< 50 mm Hg) hypotension was 26, 38 and 79%, respectively, with a mean increase of MAP in the entire group of 42%. A similar dependency existed for the systemic vascular resistance, SVR. The percent increase above baseline of SVR in the patients with moderate, severe and profound hypotension was 12%, 67% and 100% with a mean increase of 55% for the entire group. These findings appear to suggest an inverse relationship between baseline MAP and peak MAP in the presence of AVP.

The change from baseline in the dose requirements for NE are shown below :

Reference ID: 3313815

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The dosage requirements for NE after initiation of the AVP infusion were only statistically significantly lower in the group of patients with profound hypotension. However, there was a trend for reduced dose requirements of NE in the patients with severe and moderate hypotension. Relative to baseline the dose requirements for NE in the presence of AVP were reduced by -36%, -50% and -77% in the patients with moderate, severe and profound hypotension, respectively. These results suggest that the patients with moderate and severe hypotension could be weaned from NE at a relative faster rate than the patients with profound hypotension. Thus, for the claimed inverse relationship between baseline MAP and peak MAP in the presence of AVP to be true the contribution of NE to peak MAP in the presence of AVP would have to be small. The respective doses of NE tended to increase in the order moderate, severe and profound hypotension suggesting that the sensitivity to NE decreased in that order providing some support for the claimed inverse relationship between baseline MAP and peak MAP in the presence of AVP. The finding increases the relevance of this retrospective study among the submitted publications

Safety

- Was there any death or serious adverse events? ☑ Yes ☐ No ☐ NA

No episodes of malignant hypertension, mesenteric or peripheral ischemia during the postoperative period were observed. There were 3 peri-operative deaths, 1 each from sepsis, hemorrhagic shock, and multi-system organ failure.

Conclusion

- Prospective study: The incidence of vasodilatory shock is 8 %. The low levels of endogenous AVP in patients with vasodilatory shock are suggestive of AVP deficiency.
- Retrospective study: Relative to the baseline MAP the treatment with AVP increases SVR and consequently peak MAP significantly. The increase in MAP in the presence of AVP is inversely related to the respective baseline values.

Reference ID: 3313815

The percent reductions of the NE dosage requirements tend to increase in the order patients with moderate, severe and profound hypotension. The absolute doses of NE required at baseline in the patients increase in the order moderate, severe and profound hypotension suggesting that the refractoriness to NE was greatest in patients with profound hypotension suggesting the smallest contribution of NE in this group. Thus, the inverse relationship between baseline MAP and peak MAP is likely due to AVP. • Limitation: Retrospective study, open-label, uncontrolled. However, demonstration of the inverse relationship between baseline and subsequent effect by AVP on MAP suggests that the pressor effect of AVP is for real.
Comments
• None

7.3

Report #	**Study Period:** Not indicated	**EDR Link**
Title	Cutaneous Vascular Reactivity and Flow Motion Response to Vasopressin in Advanced Vasodilatory Shock and Severe Postoperative Multiple Organ Dysfunction Syndrome. Luckner G, Duenser MW, Stadlbauer K-H, Mayr VD, Jochberger S, Wenzel V, Ulmer H, Pajk W, Hasibeder WR, Friesenecker B, Knotzer H. Crit Care 2006;10:1-7	
Study Design: Prospective, randomized, controlled, open label, parallel group study in 18 patients with multiple organ dysfunction syndrome following cardiac or major surgery with a mean arterial blood pressure < 65 mm Hg despite adequate volume resuscitation, and NE requirements > 0.5 μg/kg/min. The patients were randomly assigned to receive an intravenous infusion of NE + AVP or NE.		
Rationale: Impaired microcirculatory blood flow is a key component in the pathophysiology of multiple organ failure syndrom after surgery and in sepsis. Infusions of AVP in healthy animals resulted in severe disturbances of capillary flow and tissue oxygenation. A 30% incidence of ischemic skin lesions were reported in patients with advanced vasodilatory shock receiving AVP infusions.		
Objectives: Primary: To prospectively evaluate the cutaneous microcirculatory response to a combined infusion of AVP and norepinephrine (NE) when compared with an infusion of NE alone.		
Endpoints: Primary: To evaluate differences in the AUC of the Doppler signal and the reactive hyperemic response to forearm ischemia between the AVP+NE and NE groups. Secondary: To evaluate differences in the oscillation frequency of the Doppler signal between groups		
Inclusion Criteria: patients with multiple organ dysfunction syndrome following cardiac or major surgery with a mean arterial blood pressure < 65 mm Hg despite adequate volume resuscitation, and NE requirements > 0.5 μg/kg/min.		
Exclusion Criteria: Patients with peripheral arterial vascular occlusive disease, or insulin dependent diabetes mellitus		

Reference ID: 3313815

Screening: Not indicated	**Washout:** Not applicable
Periods	Not applicable
Treatment: Constant rate intravenous infusions of NE+AVP or NE	
Sequence	Not applicable
Dose Selection: NE was titrated to maintain MAP > 65 mm Hg, AVP was infused at a rate of 0.067 IU/min	
Investigational Drugs and Formulations: Synthetic AVP (Pitressin®, Pfizer, Karlsruhe), source and identity of NE was not described by publication	
Administration: Constant rate intravenous infusion	
Fed/Fasted: Not indicated	
Interfering Substances: Not indicated	
PK Sampling Times: Blood samples for the determination of AVP or NE were not collected.	
PD Sampling Times: Immediately before and after randomization	
PD Method for measuring cutaneous vascular reactivity and flow motion: A laser Doppler flowmeter was used. Laser Doppler flowmetry has reportedly an intra- and inter-subject variability of 25% and 36%, respectively. Baseline measurements included determination of the AUC of the Doppler signal and oscillatory changes of the Doppler signal over 3 minutes (pre-ischemic). Thereafter ischemia was introduced by wrapping a sphygmanometer cuff around the brachial artery and inflating it to 300 mm Hg for 5 min. The AUC as well as the oscillatory changes during the first 3 min of reperfusion were then measured. The relative magnitude of reactive hyperemia (RH) was determined from RH= 100 ● (AUC reperfusion-AUC pre-ischemia)/AUCpre-ischemia as shown in the below figure:	
Target PK Parameters: Not applicable	
PK Data Analysis: Not applicable	
Target PD Parameters: AUC of Doppler signal, oscillation of Doppler signal pre-ischemic, oscillation of Doppler signal during reperfusion, magnitude of reactive hyperemia, MAP, cardiac index (CI), systemic O2 transport index (DO2I), systemic O2 consumption index (VO2I), mixed venous O2 saturation (SvO2), NE requirements, milrinone requirements, arterial lactate, arterial blood pH, modified Goris multiple organ dysfunction syndrome score (calculated from the worst data recorded prior to study entry)	
Statistical Method: Sample Size/Power: Demographic and clinical data characteristics of the patients were compared using Student's t-test or $\chi 2$ tests, as appropriate. To evaluate differences in hemodynamic, acid-base and microcirculatory variables between groups at baseline and over time, an unpaired Student's t-test was performed. For variables that did not fulfill the normality assumption the non-parametric Mann-Whitney U rank sum test was applied. For the detection of changes in single variables between the two measurements in each of the study groups, a paired Student's t-test was used. The selected sample size was not based on power considerations.	
Results	

Reference ID: 3313815

Study Population:

Age [Mean (SD)], years	NE+AVP	71 (9)
	NE	67 (7)
Weight [Mean (SD)], kg	NE+AVP	Not indicated
	NE	Not indicated
Male/Female	NE+AVP	6/4
	NE	5/3
Race (Caucasian/Black/Hispanic/ Asian/Other)	NE+AVP	Not indicated
	NE	Not indicated
Multiple Organ Dysfunction Syndrome score	NE+AVP	12.3 (1.1)
	NE	12.2(0.4)
ICU mortality, %	NE+AVP	80
	NE	88

Cardiovascular function could not be stabilized in 1 patients randomized to the NE group After addition of supplemental AVP MAP could be restored. This patient was therefore switched to NE+AVP group for statistical evaluation. Ten (10) patients were randomized to receive NE+AVP and 8 patients were randomized to receive NE. Ten (10) of the 18 patients were admitted to the ICU after heart surgery. Eight (8) patients were admitted because of severe systemic inflammatory response syndrome or sepsis after major abdominal (6) or thoracic (2) surgery. Time between admission to ICU and study entry was between 24 and 36 h.

The values of the variables of interest immediately before and 1 h after randomization of the patients receiving the NE+AVP or NE infusion are shown in the below table:

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PD

There was no difference between the groups in the magnitude of reactive hyperemia between the groups before and after 1 h after randomization. Patients receiving the NE+AVP had a higher oscillation frequency of the Doppler signal before ischemia and during reperfusion at study inclusion than the patients on NE. One (1) h after randomization there was no difference in the oscillation frequency before ischemia and during reperfusion between groups when adjusted for baseline differences.

Reference ID: 3313815

The patients receiving NE+AVP exhibited a significantly higher MAP and milrinone requirements than the patients receiving NE. during the observation period MAP increased significantly and the NE requirements decreased significantly in the NE +AVP group.
Safety
▪ Was there any death or serious adverse events? ☑Yes ☐No ☐ NA
Conclusion
• Supplementary infusion of AVP in patients with advanced vasodilatory shock and severe postoperative multiple organ dysfunction syndrome does not compromise cutaneous hyperemia and flowmotion when compared to NE alone
Comments
• None

7.4

Report #	**Study Period**	**EDR Link**
Title	Arginine Vasopressin in the Management of Vasodilatory Hypotension after Cardiac Transplantation. Argenziano M, Chen JM, Cullinane S, Choudhri AF, Rose EA, Smith CR, Edwards NM, Landry DW, Oz MC. J Heart Lung Transplant 1999;18:814-817	
Study Design: Retrospective study. The medical records of 150 patients undergoing orthotopic heart transplantation and receiving AVP were reviewed for cases which developed after weaning from the cardiopulmonary bypass vasodilatory hypotension with mean arterial blood pressure (MAP) < 70 mm Hg, and cardiac index (CI) > 2.5 L/min/m^2. Twenty (20) patients met these criteria. They received a constant rate AVP infusion of 0.1 U/min. Subsequently, in patients no longer requiring catecholamines, AVP infusions were weaned (reduction by 0.01 U/min every 2 h) to maintain MAP > 70 mm Hg without catecholamine support. Once the AVP infusion rate was decreased to 0.01 U/min, discontinuation of the drugs was attempted.		
Rationale: A recent publication reported on the pressor activity of AVP in patients with vasodilatory hypotension after placement of a Left Ventricular Assist Device (LVAD)		
Objectives: Primary: To study the pressor effect of vasopressin (AVP) in a related population undergoing cardiac transplantation.		
Endpoints: MAP, CI, systemic vascular resistance (SVR), central venous pressure (CVP)		
Inclusion Criteria: Patients who after weaning from cardiopulmonary bypass (CPB) developed vasodilatory hypotension with MAP < 70 mm Hg, and CI > 2.5 L/min/m^2 and needed an infusion of nor epinephrine (NE)		

Reference ID: 3313815

Exclusion Criteria: Not stated		
Screening: Not applicable		**Washout:** Not applicable
Periods	Not applicable	
Treatment: Intravenous infusion with AVP		
Sequence	Not applicable	
Dose Selection: The dose of 0.1 U/min AVP was used in a previous study without overt toxicity		
Investigational Drugs and Formulations: Pitressin (Parke-Davis) was used. The publication does not state that AVP was dissolved in isosaline for infusion.		
Administration: Intravenous		
Fed/Fasted: Not stated, presumably fasted		
Interfering Substances: NE, milrinone, dobutamine, nitroglycerine		
PK Sampling Times: No blood samples were collected for the determination of the plasma concentrations of AVP		
PD Sampling Times: Pre dose and 1 and 2 h after AVP infusion initiation		
Analytical Method: Not applicable		
Target PK Parameters: Not applicable		
PK Data Analysis: Not applicable		
Target PD Parameters: MAP, CVR, CVP, CI		
Statistical Method: Paired variables were analyzed using the paired Student's t-test, unpaired variables were compared by the Wilcoxon non-parameteric test, and correlation coefficients were calculated for linear relationships. **Sample Size/Power:** The goal of the study is to provide preliminary information. Therefore, the selected sample size is not based on power considerations.		
Results		

Study Population:

Treated	20
Completed	20
Discontinued	0
Pharmacodynamic population	20
Safety population	20
Age [Mean (SD)], years	Not indicated
Weight [Mean (SD)], kg	Not indicated
Male/Female	Not indicated
Race (Caucasian/Black/Hispanic/ Asian/Other)	No indicated

PD

The AVP infusions were instituted from 10-240 min after weaning from cardiopulmonary bypass (CPB). The duration of the AVP infusions ranged from 2 h to 3 d. The mean values for the hemodynamic parameters of the patients prior to and 1 and 2 h after initiation of the AVP infusions are listed in the below table:

Reference ID: 3313815

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The results indicate that MAP relative to baseline increased 26 and 25 mm Hg 1 and 2 h, respectively, into the AVP infusions. The corresponding values for SVR increased by 720 and 820 dyne-sec/cm^5 after 1 and 2 h after initiation of the AVP infusions. The dose requirements for NE decreased by 35 and 45%, respectively, 1 and 2 h after start of the AVP infusions. There was an inverse relationship between change in MAP and baseline MAP. Patients with severe hypotension (MAP< 60 mm Hg) displayed an increase in MAP of 32 (4) mm Hg whereas patients with moderate hypotension (MAP > 60 mm Hg) showed an increase in MAP of only 20 (3) mm Hg. In at least 5 cases initial attempts to wean AVP resulted in hypotension. There were no episodes of mesenteric or peripheral ischemia or malignant hypertension with the AVP infusion regimen.

Safety

- Was there any death or serious adverse events? ☑ Yes ☐No ☐ NA
- There was 1 peri-operative death occurring on Day 21, due to hemorrhagic shock and multi-system failure.

Conclusion

- Infusions of 0.1 U/min AVP increase MAP and SVR significantly and reduce the dosage requirements for NE 1 and 2 h after initiation relative to baseline.

Comments

- None

7.5

Reference ID: 3313815

Report #	Study Period:January 1998- January 2001	EDR Link
Title	Cardiac Performance During Vasopressin Infusion in Post-Cardiotomy Shock. Duenser MW, Mayr AJ, Stallinger A, Ulmer H, Ritsch N, Knotzer H, Paijk W, Mutz NJ, Hasibeder WR. Intensive Care Med 2002:28:746-751	

Study Design: Retrospective. Patients with catecholamine resistant shock on norepinephrine (NE) received AVP infusions to keep mean arterial blood pressure (MAP) ≥ 60 mm Hg. When MAP exceeded 60 mm Hg was stepwise decreased according to MA. NE was not completely withdrawn in any patient. AVP infusion was continuously reduced and tapered off when NE requirements fell below a dose of 0.3-0.4 µg/kg/min. In this situation weaning from AVP occurred first and individually according to the patient's response to the stepwise decrease of AVP.

Rationale: Cardiac safety of AVP insufficiently determined. In earlier times AVP in high doses was used as a stress test to provoke ischemic ECG changes.

Objectives: Primary: Determination of cardiac performance, biomarkers of myocardial ischemia, and systemic hemodynamics in catecholamine resistant post-cardiotomy shock

Screening: Not applicable	Washout: Not applicable

Periods	Not applicable

Treatment: Intravenous infusions of 0.067- 1.0 U/min AVP

Sequence	Not applicable

Dose Selection: High infusion rates to evaluate possibly toxic effects of AVP on heart

Investigational Drugs and Formulations: Pitressin®, Parke-Davis, Berlin, Germany

Administration: Intravenous infusion

Endpoints: MAP, heart rate (HR), heart rhythm, central venous pressure (CVP), mean pulmonary arterial pressure (MPAP), cardiac index (CI), left ventricular stroke work index (LVSWI), systemic vascular resistance (SVR), dosage requirements for NE and milrinone (M)

Inclusion Criteria: Volume resuscitated patients after undergoing cardiotomy with catecholamine resistant shock (failing effect of stepwise increase of NE 0.2 µg/kg/min over a 2 h period to keep MAP ≥ 60 mm Hg)

Fed/Fasted: Not stated

Interfering Substances: Not stated

PK Sampling Times: No samples for determining PK of AVP were collected

PD Sampling Times: 0, 1, 4, 12, 24 and 48 h after initiation of AVP infusion

Analytical Method: Not applicable

Target PK Parameters: Not applicable

PK Data Analysis: Not applicable

Target PD Parameters: MAP, HR, arrhythmias, CVP, CO, PMAP, SVR, LVSWI, dosage requirements for NE and M. Postoperative new-onset tachyarrythmia (TA) was defined as a non-sinus rhythm (SR) exceeding 100 bpm were recorded by continuous ECG monitoring. Creatine kinase MB (CKMB) and troponin- I (TROP) were measured at baseline after cardiotomy and a least once per day in the ICU.

Statistical Method:
Sample Size/Power: Repeated measurements were analyzed using a mixed effects model. In order to account for death related drop-outs. Parameters which did not meet normality assumptions (PVR, CKMB, TROP) were log transformed. If trends were significant

Reference ID: 3313815

comparisons versus baseline were performed using the same model. Due to the exploratory character of the study no corrections for multiple comparisons were used. Therefore the selected sample size is not based on power considerations.

Results

Study Population:

The demographics of the patients are shown below:

Treated Completed Discontinued subject Pharmacodynamic population Safety population	41 21 20 41 41
Age [Mean (SD)], years	71 (8)
Weight [Mean (SD)], kg	Not indicated
Male/Female	30/11
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated

The disease characteristics of the study population are summarized in the below table:

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PD

The mean (AD) duration of the AVP infusion was 64 (56) h. The ICU mortality in patients with post-cardiotomy shock was 54%, In contrast, overall mortality from elective cardiac surgery was 3% and from emergency cardiac surgery 27% during the observation period. The cardiac parameters and hemodynamic results are shown in the below table:

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The infusion with AVP increased significantly MAP, SVR and LVSWI, and reduced significantly HR. No changes were observed in CI and SVI. The dose requirements for NE and M decreased significantly by 55 and 18%, respectively. CKMB and TROP fell significantly in all patients with increased serum concentrations at study entry and remained low in patients without postoperative serum elevations. Twenty-two (22) patients experienced TA at study entry or during the observation period (AFIB 91%, regular, non-SR tachycardia 9%. Ten (10) patients (46%) converted to SR during AVP infusion. Six (6) patients were already receiving a continuous infusion of amiodarone for ≥ 6 h before start of AVP infusion or did not receive any antiarrhythmic therapy (sentence does not make sense). Three (3) patients developed new-onset AFIB during AVP infusion.

Safety

- Was there any death or serious adverse events? ☑Yes ☐No ☐ NA

Conclusion

- Infusion with AVP (0.067-0.1 U/min) increased significantly MAP, SVR and LVSWI, and reduced significantly HR. NE and M requirements were significantly reduced. No changes were observed in CI and SVI. Forty six (46) % new onset TA converted into SR. CKMB and TROP fell during the AVP infusions.
- No overt ischemic or arrhythmic cardiac effects of AVP were observed.

Comments

None

Reference ID: 3313815

7.6

Report #	**Study Period: Jan 1995- Aug 1998**	**EDR Link**
Title	Arginine Vasopressin in the Treatment of 50 Patients with Post-cardiotomy Vasodilatory Shock. Morales DLS, Gregg D, Helman DN, Williams MR, Naka Y, Landry DW, Oz MC. Ann Torac Surg 2000;69:102-106	
Study Design: Retrospective study using the medical records of 102 patients receiving Left Ventricular Assistance Devices (LVAD) implantations. Fifty (50) patients were eligible for the study based on a history of vasopressin (AVP) administration in the operating room or ICU within 24 h of implantation.		
Rationale: Anecdotal evidence for pressor effect of AVP in post-cardiotomy shock exists, but a larger data base is needed to evaluate the utility of AVP in this patient population.		
Objectives: Primary: To report overall experience with AVP as a treatment for post LAVD vasodilatory shock		
Endpoints: Mean arterial blood pressure (MAP), systemic vascular resistance (SVR), pulmonary artery blood pressure (PAP)		
Inclusion Criteria: Not stated		
Exclusion Criteria: Not stated		
Screening: Not applicable		**Washout:** Not applicable
Periods	Not applicable	
Treatment: Intravenous infusion of AVP		
Sequence	Not applicable	
Dose Selection: 0.09 (0.05) U/min AVP starting dose		
Investigational Drugs and Formulations: Identity and manufacturer of AVP are not indicated in the publication. The publication does not state that AVP was dissolved in isosaline for infusion.		
Administration: Intravenous		
Fed/Fasted: Not stated, presumably fasted		
Interfering Substances: Co-administered norepinephrine (NE), milrinone, dobutamine, dopamine, epinephrine		
PK Sampling Times: Blood samples were not collected for the determination of the plasma concentrations of AVP		
PD Sampling Times: 15 min before and after start of the AVP infusion.		
Analytical Method: Not applicable		
Target PK Parameters: Not applicable		
PK Data Analysis: Not applicable		
Target PD Parameters: MAP, SVR, PAP, LVAD flow		
Statistical Method: Sample Size/Power: All data comparisons were done using a paired two-tailed Student's t-test. The goal of the study is to provide preliminary information. Therefore, the selected sample size is not based on power considerations.		
Results		

Reference ID: 3313815

Study Population:

Treated Completed Discontinued Pharmacodynamic population Safety population	50 50 0 50 50
Age [Mean (SD)], years	52(15)
Weight [Mean (SD)], kg	Not indicated
Male/Female	42/8
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated

PD

The apparent effects of AVP on the hemodynamic parameters are listed in the below table:

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Within 15 min after initiation of the AVP infusion MAP and SVR increased by 17 mm Hg and 280 dynes/sec/cm^3 relative to baseline whereas PAP and LVAD flow remained unchanged. The dosage requirements of NE decreased by 32% relative to baseline, whereas the requirements for milrinone, dobutamine, dopamine and epinephrine did not change as shown in the below table:

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The mean (SD) length of the AVP infusions was 7 (12) days with no evidence of

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tachyphylaxis.
Safety
▪ Was there any death or serious adverse events? ☑Yes ☐ No ☐ NA The post-implantation complications are shown in the below table: COPYRIGHT MATERIAL Five patients developed new renal insufficiency. Four (4) of these 5 patients recovered. All 5 patients who died had pre-existing renal insufficiency (4) or developed renal insufficiency (1). Digital or distal limb ischemia was seen in 3 patients.
Conclusion
PD • The pressor effect of AVP was seen within 15 min after start of the infusion as raises in MAP and SVR. • There was no evidence for tachyphylaxis of the hemodynamic effect of AVP **Safety** • Digital or distal limb ischemia was seen in 6% of the patients **Limitation** • Retrospective study
Comments
• None

8. Shock of Mixed Etiology (PS, SS, SIRS)

8.1

Report #	**Study Period:** January 1999 - December 31, 2003	**EDR Link**
Title	Arginine Vasopressin in 316 Patients with Advanced Vasodilatory Shock. Luckner G, Duenser MW, Jochberger S, Mayr VD, Wenzel V, Ulmer H, Schmid S, Knotzer H, Pajk W, Hasibeder W, Mayr AJ, Friesenecker B. Crit Care Med 2005 33:2659-2666	
Study Design: Retrospective Study. Between January 1999 and December 2003 a cohort of 316 patients with advanced vasodilatory shock admitted to the 23 bed ICU of this tertiary		

Reference ID: 3313815

teaching hospital and receiving supplemental vasopressin (AVP) has been analyzed. Patients were grouped into 1) Patients with septic shock 2) Patients with post-cardiotomy shock and 3) Patients with vasodilatory shock due to overwhelming systemic inflammatory response syndrome (SIRS). The syndromes of sepsis and SIRS were defined in accordance with to the American of Chest Physicians/Society of Critical Medicine Consensus Conference criteria. Age admission diagnoses, length of stay in ICU and AVP infusion, simplified Acute Physiology Score II, most severe multiple organ dysfunction syndrome score and ICU mortality were documented. All patients with vasodilatory shock were managed according to an institutional hemodynamic protocol with fluid resuscitation until the stroke volume (SV) could not be further increased. Central venous and arterial occlusion pressures were used to guide fluid resuscitation. If the SV remained < 25 mL/beat/m^2 or cardiac index (CI) was < 2.0 L/min/m^2, milrinone was started as a continuous infusion (0.3-0.7 µg/kg/min). An additional epinephrine infusion (0.05-0.3 µg/kg/min as administered only in patients with severe cardiac failure and who did not achieve a CI of > 2 L/min/m^2. If the mean arterial pressure (MAP) remained at < 70 mm Hg, a norepinephrine (NE) infusion was started. And in 218 of 316 patients a continuous hydrocortisone infusion (200-300 mg/day) was administered. If a stepwise increase of 0.2 µg/kg/min NE in 2 h did not restore MAP, AVP was started as a supplementary continuous infusion. The norepinephrine infusion rate was then adapted to maintain the MAP at > 70 mmHg. If the NE infusion could be decreased to < 0.3 µg/kg/min the AVP infusion was slowly tapered off in accordance with response of the blood pressure.	
Rationale: Numerous reports indicate beneficial effects of AVP administration in vasodilatory shock. Concerns have been raised because of possible adverse events caused by AVP and lack of knowledge about the right time of initiating infusions with AVP.	
Objectives: Primary: Study results provide information allowing clinicians to improve care of patients with vasodilatory shock	
Endpoints: Heart rate (HR), MAP, central venous pressure (CVP), mean pulmonary arterial blood pressure (MPAP), CI, stroke volume index (SVI), and pulmonary artery occlusion pressure (PAOP) and cardiovascular drug dosage requirements.	
Inclusion Criteria: Patients with septic shock 2) Patients with post-cardiotomy shock and 3) Patients with vasodilatory shock due to overwhelming systemic inflammatory response syndrome. The syndromes of sepsis and SIRS were defined in accordance with the American of Chest Physicians/Society of Critical Medicine Consensus Conference criteria.	
Exclusion Criteria: Not stated	
Screening: Not indicated	**Washout:** Not applicable
Periods	Not applicable
Treatment: AVP at a rate of 0.067 U/min	
Sequence	Not applicable
Dose Selection: Previous studies suggest that AVP at an infusion rate of 0.067 is tolerated	
Investigational Drugs and Formulations: Synthetic AVP, Pitressin®, Pfizer, Karlsruhe, Germany. The publication does not state that AVP was dissolved in isosaline for infusion.	
Administration: Constant intravenous infusion of AVP	
Fed/Fasted: Not indicated	
Interfering Substances: Not indicated	
PK Sampling Times: No blood samples for AVP or the other administered drugs were collected	

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PD Sampling Times: • Hemodynamic variables: Pre-dose, 0.5, 1, 4, 12, 24, 48, and 72 h after start of AVP infusion • Laboratory Variables: pre-dose, 24, 48 and 72 h after start of the AVP infusion
Analytical Method: Not applicable
Target PK Parameters: Not applicable
PK Data Analysis: Not applicable
Target PD Parameters • HR, MAP, CVP, MPAP, CI, SVI, PAOP and cardiovascular drug dosage requirements • pH, arterial lactate, serum creatinine, aspartate- and alanine aminotransferases, total bilirubin, $Pa0_2/FI0_2$ quotient, platelet count, phophocreatine kinase, troponin I • Adverse hemodynamic or laboratory events occurring during the AVP infusion
Statistical Method/Sample Size/Power: Shapiro-Wilk's tests were used to check for normality of distribution of data, which was approximately fulfilled by all data with the exception of the values for aspartame- and alanine aminotransferases, total bilirubin, platelet count, arterial lactate, phosphocreatine kinase which were log transformed. The goal of the study is to provide preliminary information. The repeated measurements and differences between patients with septic, post-cardiotomy or SIRS related shock were analyzed with a mixed-effect model. If time effects were significant, comparisons vs. baseline were performed using the same model. Demographic, hemodynamic and laboratory and drug dosages before initiation of the AVP infusions were entered into a bivariate correlation model to test for univariate differences between patients with vs. patients without the observed adverse event. The differences in mortality between patients with vs without the adverse side effect were analyzed using the Fisher's exact test. Independent risk factors for death from advanced vasodilatory shock treated with AVP were analyzed using the same model. Because of its skewed distribution , the variable NE requirements before start of AVP therapy was grouped into three clinically relevant dosage steps 0-0.5, 0.5-1.0 and >1.0 µg/kg/min and then entered into the statistical model.
Results

Reference ID: 3313815

Study Population:

The below table lists demographics and baseline characteristic of the patients:

Treated Septic shock Postcardiotomy shock Shock due to overwhelming SIRS Safety population	316 103 135 78 316
Age [Mean (SD)], years	67(14)
Weight [Mean (SD)], kg	Not indicated
Male/Female	Not indicated
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated
Simplified Physiology Score II	46.7(15.2)
Multiple Organ Dysfunction Score	11.1(15.2) points equivalent to 5.6 failed organs
Mean Stay in ICU	17.8 (15.5) days
Mortality	50.9%
On continuous veno-venous hemofiltration (CVVHF)	79

Hemodynamic Responses to AVP

The below table lists the mean (SD hemodynamic variable at baseline and during the AVP infusions:

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HR, CVP and MPAP significantly decreased during the AVP infusion. In contrast, MAP, SVI, and SVR increased. Norepinephrine, milrinone, and epinephrine dosage requirements were significantly reduced during the 72 h observation period. There were no significant differences in the hemodynamic response to AVP in the patients with septic-, post-cardiotomy- or SIRS related shock. Changes in HR and MAP appear to occur as early as 0.5 h after initiation of the AVP infusions. However, because of the changes in the dosage of NE permitted per protocol

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an assessment of when the peak effect of AVP occurs is not possible.

Laboratory Responses to AVP

The next table lists the mean (SD) laboratory values at baseline and during the infusions with AVP:

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The pH, aspartate- and alanine aminotransferases and total bilirubin increased whereas arterial lactate concentrations and platelet count decreased. The observed increase in bilirubin and the decrease in platelet were due to the patients on CVVHF.

Safety

- Was there any death or serious adverse events? ☑Yes ☐ No ☐ NA

Adverse Event Responses to AVP

Table 3 presents the results of the statistical analysis:

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Significant changes included that CI decreased with no relationship to mortality, total bilirubin and serum transaminases increased and platelet count decreased.
Conclusions
• Relative to baseline HR, CVP and MPAP decreased and MAP, SVI, and SVR increased during the supplementary AVP infusions. • The co-administration of AVP reduced the dosage requirements for NE and milrinone. • pH, aspartate- and alanine aminotransferases and total bilirubin increased, whereas arterial lactate concentrations and platelet count decreased. The observed increase in bilirubin and the decrease in platelets were due to the patients on CVVHF. • Limitation: This a retrospective study, and the results must be interpreted with caution.
Comments
• None

8.2

Report #	**Study Period**: January 1, 1999-December 31, 2003 and January 1, 2004-December 31, 2006	**EDR Link**
Title	Comparison of Two Dose Regimens of Arginine Vasopressin in Advanced Vasodilatory Shock. Luckner G, Mayr VD, Jochberger S, Wenzel V, Ulmer H, Hasibeder WR, Duenser MW. Crit Care Med 2007;2280-2285	
Study Design: Retrospective controlled study. An institutional database including all patients treated with AVP at the 12 bed general and surgical ICU of a tertiary university teaching hospital from January 1911 to December 31, 2006 was utilized. First the vasopressin (AVP)		

Reference ID: 3313815

database was searched for patients with vasodilatory shock who received AVP at 0.033 IU/min during from January 1, 2004 to December 31, 2006. Subsequently a comparable historic group of patients with vasodilatory shock treated with AVP at 0.067 IU/min was extracted from the same database. With descending priority patients receiving AVP at 0.067 IU/min were matched in a blinded fashion with the study population receiving 0.033 IU/min based on norepinephrine (NE) requirements and mean arterial blood pressure (MAP) before start of the AVP infusion, severity of multiple organ dysfunction syndrome, age, milrinone and epinephrine dosages. All patients with vasodilatory shock were managed according to an institutional hemodynamic protocol with fluid resuscitation until the stroke volume (SV) could not be further increased. Central venous pressure (CVP and pulmonary artery occlusion pressure (PAOP) were used to guide fluid resuscitation. If the SV remained < 25 mL/beat/m^2 or cardiac index (CI) was < 2.0 L/min/m^2, milrinone was started as a continuous infusion (0.3-0.7 µg/kg/min. An additional epinephrine infusion (0.05-0.3 µg/kg/min as administered only in patients with severe cardiac failure and who did not achieve a CI of > 2L/min/m^2. If the MAP remained at < 65-70 mm Hg, a NE infusion was started. If a stepwise increase of 0.2 µg/kg/min in 2 h did not restore MAP, AVP was started as a supplementary continuous infusion. The NE infusion rate was then adapted to maintain the MAP at > 70 mmHg. If the NE infusion could be decreased to < 0.3 µg/kg/min the AVP infusion was slowly tapered off in accordance with response of the blood pressure.	
Rationale: There are no data on the appropriate AVP dosage in patients with vasodilatory shock. Beneficial effects were reported for AVP with infusion rates of 0.02-0.067 U/min. Detrimental effects of AVP have been reported for dosages of up to 1.8 U/min.	
Objectives: To compare the effects of commonly applied AVP dose regimens, namely 0.033 and 0.067 IU/min on efficacy, hemodynamic response, prevalence of adverse events, and changes in laboratory variables in patients with advanced vasodilatory shock.	
Inclusion Criteria: Vasodilatory shock**,** defined as cardiovascular failure with lowered systemic vascular resistance requiring vasopressor therapy, secondary to sepsis, status after cardiac surgery or due to overwhelming systemic inflammation after major surgery.	
Exclusion Criteria: Age < 18 years, AVP infusions not related to treatment of vasodilatory shock	
Endpoints: Primary: To evaluate the difference in treatment efficacy and the hemodynamic responses between the two AVP dose regimens of 0.033 and 0.067 IU/min. Secondary: To evaluate the difference in the prevalence of adverse events and changes in the laboratory variables between the groups. Prevalence and extent of an increase of MAP within 30 min after start of the AVP infusions was used as efficacy parameter in combination with the extent of NE requirements during the first 24 h of the AVP infusions.	
Screening: Not applicable	**Washout:** Not applicable
Periods	Not applicable
Treatment: Constant Intravenous infusions at rates of 0.033 and 0.067 IU/min	
Sequence	Not applicable
Dose Selection: Infusions of AVP 0.033 and 0.067 IU/min have been shown to be tolerated and exhibit beneficial effects in previous studies	
Investigational Drugs and Formulations: Source and identity of AVP are not indicated in the publication. The publication does not state that AVP was dissolved in isosaline for infusion.	
Administration: Constant intravenous infusion at two different rates of 0.033 and 0.067	

Reference ID: 3313815

IU/min AVP
Fed/Fasted: Not indicated
Interfering Substances: Not indicated
PK Sampling Times: Blood samples for the determination of AVP in plasma were not collected
PD Sampling Times: Hemodynamic variables [heart rate (HR), MAP, CVP, mean pulmonary arterial blood pressure (MPAP), pulmonary artery occlusion pressure (PAOP), CI, stroke volume index (SVI), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), NE-, milrinone, epinephrine requirements were measured: At baseline and 0.5, 1, 4, 12, 24, 48 and 72h after initiation of the infusion Organ function variables included serum aspartate- and alanine aminotransferases, total bilirubin, creatinine, and platelet count were collected: At baseline and 4, 12, 24, 48 and 72 h after AVP infusion start Base deficit, pH, and arterial lactate levels were obtained at baseline, and 1, 4, 12, 24 and 72 h after initiation of the infusions.
Analytical Method None of the assays used for measuring laboratory variables were indicated in the publication. AVP concentrations were not measured in this study.
Target PK Parameters: Not applicable
PK Data Analysis: Not applicable
Target PD Parameters • Hemodynamic variables including heart rate (HR), MAP, CVP, MPAP, PAOP, CI, SVI, SVR, PVR and NE-, milrinone, and epinephrine requirements • Organ function variables including serum aspartate and alanine aminotransferases, total bilirubin, creatinine, and platelet count • Base deficit, pH, and arterial lactate levels
Statistical Method/Sample Size/Power: Normality distribution was checked by the Kolgomorov-Smirnov test. Unpaired Student's t-test for normally distributed continuous variables and Fisher's exact test for categorical variables, or Mann-Whitney U rank-sum tests for not normally distributed continuous variables (e.g. duration of AVP infusion, length of stay in the ICU) were used to compare demographic and clinical variables between study groups. A mixed effects model was used to account for death-related drop-outs. In case of significant differences between groups, the same model was used to test for changes over time within single study groups. The goal of the study was to provide preliminary information. Therefore the selected sample size is not based on power considerations.
Results

Reference ID: 3313815

Study Population:

The below table lists the demographics and clinical data of the evaluated patients:

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The characteristics were comparable except that in the group receiving 0.067 IU/min AVP females exceeded males substantially and the multiple organ dysfunction score was slightly, but significantly greater than in the group receiving 0.033 U/min AVP.

The mean (SD) hemodynamic variables in the patients receiving AVP at a rate of 0.033 or 0.067 IU/min are presented in the below table:

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PD

Patients treated with 0.033 IU/min received AVP for a significantly shorter time interval than the patients receiving the treatment with 0.067 IU/min. The respective lengths of the infusion durations are not indicated.

Hemodynamic Variables

Mean increase and prevalence of MAP in the first 30 min after infusion start were not different among the groups**.**

Relative to baseline the respective mean (SD) increase in MAP was 16.88 (18.4) and 21.4 (14.9) mm Hg in patients treated with 0.033 and 0.067 IU/min AVP. During the first 24 h after infusion start the NE infusions could be reduced significantly more often in patients receiving 0.067 U/min AVP than in patients receiving the 0.033 IU/min as shown in the below figure:

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The changes in MAP appear to occur as early as 0.5 h after initiation of the AVP infusions. However, because of the changes in the dosage of NE permitted per protocol an assessment of when the peak effect of AVP occurs is not possible.

Other hemodynamic variables that varied significantly between the groups included MPAP and CVP which were smaller in the group receiving 0.033 IU/min AVP than in the group treated with 0.067 IU/min AVP, whereas the NE requirements were increased in the group receiving 0.033 IU /min AVP. HR decreased only in the 0.067 IU/min group, whereas MAP increased in both groups. PAOP and SVR (only up to 24 h) increased both in the group receiving 0,033 IU/min. Relative to baseline the NE dosage requirements increased up to 24 h in the group receiving 0.033 IU/min AVP, but decreased in the 0.067 IU/min receiving group.

Laboratory Variables

The below table lists the mean (SD) laboratory values of the two groups:

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Safety

- Was there any death or serious adverse events? ☑Yes ☐ No ☐ NA death occurred, but the mortality rate is not reported.
- An increase in serum aminotransferases occurred more frequently with the 0.033 U/min infusion rate. Compared to baseline, the platelet count decreased significantly in both groups. Bilirubin increased in the group receiving 0.067 IU/min AVP. Arterial lactate concentrations increased in the group receiving 0.033 IU/min and decreased in the group receiving 0.067 IU/min. In contrast, base deficit increased in the patients receiving 0.067 IU/min and decreased in the patients receiving 0.033 IU/min.

Conclusion

- Relative to baseline a comparable mean increase in MAP is observed in the groups receiving AVP at an infusion rate of 0.033 or 0.067 IU/min.
- The dosage of NE can be reduced significantly more often in patients receiving the 0.067 U/min regimen. AVP infused at 0.067 IU/min raises MAP, and lowers CVP and NE requirements during the 72 observation period.
- The increase in MAP occurs as early as 0.5 h after initiation of the AVP infusions
- AVP dosages of 0.067 IU/min appear to be more effective in reversing cardiovascular failure in vasodilatory shock requiring high NE dosages than 0.033 U/min.
- Total bilirubin levels and base deficit are lower and arterial lactate concentrations higher in the patients receiving 0.033 IU/min AVP.
- The limitations: The study is retrospective in design. The result may be that changes in the management of the patients occurring between the periods of 1999-2003 and 2004-

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	2006 and differences in baseline characteristics among the groups (difference in number of subjects of female and male sex and severity of multiple organ dysfunction) are significantly underestimated.
Comments	
None	

8.3

Report #	Study Period: January 1- December 31 2008	**EDR Link**
Title	Comparing Two Different Arginine Vasopressin Doses in Advanced Vasodilatory Shock: A Randomized, Controlled, Open-Label Trial. Torgersen C, Duenser MW, Wenzel V, Jochberger S, Mayr V, Schmittinger CA, Lorenz I, Schmid S, Westphal M, Grander W, Luckner G. Intensive Care Med 2010'36:57-65	
Study Design: In this randomized, controlled, open-label trial patients with vasodilatory shock due to sepsis, systemic inflammatory response syndrome or after cardiac surgery requiring norepinephrine >0.6 µg/kg/min were randomized to receive a supplementary AVP infusion either at 0.033 U/min or 0.067 U/min. The trial was conducted in a general and surgical intensive care unit (ICU) of a single center, a 23-bed tertiary teaching hospital. The authors hypothesis was that treatment with 0.067 U/min AVP could restore hemodynamic stability more effectively than 0.033 U/min.		
Rationale: Even though the Vasopressin in Septic Shock Trial (VASST) showed no benefit of a supplementary infusion of AVP infused at rates between 0.01-0.03 U/min on septic shock survival the latest guidelines, the Surviving Sepsis Campaign suggests that AVP at an infusion rate of 0.03 U/min may be added as an adjunct vasopressor agent when hemodynamic instability persists despite escalating norepinephrine (NE)doses. Although several clinical trials have been conducted using infusion rates of between 0.01 and 2.0 U/min AVP in the past little is known about the optimal dosing of vasopressin. No prospective comparison of different infusion rates of AVP has been conducted.		
Objectives: Primary: To compare the effects of AVP infused at 0.033 U/min and 0.67 U/min		
Endpoints: Primary: Difference in hemodynamic response to AVP infusions at rates of 0.033 and 0.067 U/kg. Secondary: Differences in organ function and laboratory variables AVP and prolactin plasma levels as well as the rate of adverse events**.** Heart rate (HR), MAP, central venous pressure (CVP), mean pulmonary arterial pressure (MPAP), pulmonary arterial occlusion pressure (PAOP), cardiac index, stroke volume index and mixed venous oxygen saturation. Norepinephrine, epinephrine, and milrinone requirements were documented at the same times.		
Inclusion Criteria: Patients with vasodilatory shock due to sepsis, systemic inflammatory response syndrome (SIRS) or cardiac surgery requiring norepinephrine>0.6 µg/kg/min to maintain mean arterial blood pressure (MAP) > 60 mm Hg**.** Patients had to be included within 12 h after their NE demand exceeded 0.6 µg/kg/min or within 12 h after ICU admission (in case NE doses exceeded 0.6 µg/kg/min before ICU admission). Platelet count, ALT AST, Total bilirubin, creatinine, urea, troponin T, AVP and prolactin in plasma were measured before 24 and 48 h after AVP infusion start. Hemoglobin, arterial pH, lactate, base deficit and partial arterial oxygen tension /fractional inspiratory oxygen concentration ratio were recorded before, 1,12, 24, and 48 h after randomization. Occurrence of adverse events (>5% increase in liver enzymes or total biblirubin levels or > 5% decrease in platelet count or cardiac index durig the 48 h observation		

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period compared to randomization values) was evaluated in all study participants. Vasodilatory shock was defined as the simultaneous presence of adequate systemic blood flow, CI >2-2.5 L/min/m2, mixed venous oxygen saturation > 60%, or an ejection fraction >50% together with a heart rate > 80 bpm in the absence of severe diastolic dysfunction on echocardiography), MAP < 60 mm Hg in volume resuscitated patients together with a systemic vascular resistance index <1200 dyne●s/cm^5●m^2 resulting in the need for NE> 0.1 µg/kg/min for > 12 h. Sepsis and SIRS were defined in accordance with the criteria of the American College of Chest Physicians and the Society of Critical Medicine (1)	
Exclusion Criteria: Patients < 18 years, moribund unlikely to survive > 12 h, in whom intensive care therapy was withdrawn or limited in an end-of-life decision, who received AVP or any of its analogues because of other diagnoses than vasodilatory shock, participated in another trial, were pregnant or effused written informed consent	
Screening: Not applicable	**Washout:** Not applicable
Periods	Not applicable
Sequence	Not applicable
Dose Selection: Vasopressin at infusion rates of 0.033 and 0.067 U/min have been shown to exhibit pharmacological effects and are safe	
Investigational Drugs and Formulations: Pressyn® (Ferring Inc., Toronto, Canada) Publication does not state that AVP was dissolved in isosaline for infusion.	
Administration: Intravenous infusion	
Fed/Fasted: Not indicated	
Interfering Substances: Corticosteroids	
PK Sampling Times: Pre-dose, 24 and 48 h	
PD Sampling Times: Pre-dose, 1, 12, 24 and 48 h after randomization	
Analytical Methods Blood samples for the determination of the plasma levels of AVP and prolactin after centrifugation were frozen immediately at -70 ˚ C until assaying. The AVP concentrations were measured using the radioimmunoassay of DRG Diagnostics, Marburg, Germany. Prolactin was measured by an enzyme-linked immunosorbent assay of DRG Diagnostics, Marburg, Germany.	
Target PK Parameters: Css; CL not calculated because of unknown potency of AVP Ferring	
PK Data Analysis: Dose proportionality, possible impact of hydrocortisone on exposure to AVP	
Target PD Parameters: HR, MAP, CVP, MPAP, PAOP, cardiac index, stroke volume index and mixed venous oxygen saturation, NE, epinephrine, and milrinone requirements prolactin plasma levels,	
Statistical Method: Normality distribution was tested by the Kolmogorov-Smirnov test. Incase the normality assumption did not hold the variables were ln transformed. All group comparisons were performed as intent to treat analyses. The unpaired Student's t-test (continuous) or Fisher's exact test (categorical) was compared and clinical parameters as well as the rate of adverse events between groups. A linear mixed effects model was used to account for drop-outs during the observation period when the hemodynamic response , changes in laboratory parameters as well as laboratory variables were compared among the 0.033 and 0.67 U/min AVP infusion rates. If hemodynamic and laboratory variables showed group differences (p<0.01) before randomization, the baseline value of the corresponding variable was the baseline values of the corresponding variable and entered	

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as covariate into the mixed effects model.
Sample Size/Power: Based on the results of a previous study a sample size of 22 subjects per group was required to detect a significant difference in MAP increase and norepinephrine decrease (alpha error 0.05, beta error 0.2, power 80%).

Results

Study Population:

Fulfilled Inclusion Criteria		61
Fulfilled Exclusion Criteria		11
Randomized		50
Treated	AVP 0.033 U/min	25
Completed & Analyzed	AVP 0.033 U/min	25
Treated	AVP 0.067 U/min	25
Completed & Analyzed	AVP 0.067 U/min	25
Pharmacokinetic population		50
Safety population		50

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The baseline characteristics of the patients randomized to the 2 AVP treatments were comparable. Thirteen (130 and 14 patients received hydrocortisone in the groups infused with 0.033 U/min and 0.067U/min, respectively.

PK

The below figures and tables show the plasma concentration of AVP and prolactin:

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The plasma concentrations of AVP before and during the infusions with rates of 0.033 U/min and 0.067 U/min are shown in the below table for all patients whether they received hydrocortisone or not:

Mean (SD) Plasma Concentrations of AVP prior to and 24 and 48 h into the AVP Infusions at Rates of 0.033 and 0.067 U/min

AVP Infusion Rate	$C_{baseline}$	$C_{24\ h}$	$C_{48\ h}$
U/min	pmol/L		
0.033	15.9 (24.7)	114.7 (56.2)	98.8 (46.0)
0.067	13.9 (6.3)	262.0 (138.2)	216.5 (125.7)

The plasma concentrations of AVP in the subjects receiving hydrocortisone and those who did not prior to and 24 and 48 h into the AVP infusions are listed in the below table:

Mean (SD) Plasma Concentrations of AVP prior to and 24 and 48 h into the AVP Infusions at Rates of 0.033 and 0.067 U/min in the Group of Patients who received Hydrocortisone and in the Group of Patients who did not [a]

Hydrocortisone Co-Administration	AVP Infusion Rate	$C_{baseline}$	$C_{24\ h}$	$C_{48\ h}$
	U/min	pmol/L		
No	0.033	9.8 (7.9)	103.3 (72.8)	100.6 (56.1)
Yes	0.033	21.5 (33.1)	123.9 (39.2)	97.3 (39.3)
No	0.067	12.5 (5.9)	216.5 (128.1)	191.9 (123.1)
Yes	0.067	15.1 (6.7)	318.9 (136.6)	234.9 (132..8)

[a] The plasma concentrations of AVP were read off Figure 2 of the publication

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In order to extract form the above crude data whether the PK of AVP are dose proportional and whether hydrocortisone impacted AVP at both dose levels the Reviewer conducted a more detailed analysis the results of which are shown in the below 2 tables:

Hydrocortison Co-administration	Ratio of Concentrations of AVP in Group Receiving AVP Infusion Rate of 0.067 U/min to Concentrations in Group Receiving AVP Infusion Rate of 0.033 U/min[a]	
	24 h	48 h
No	1.1	0.99
Yes	1.6	1.5

[a] The concentrations of AVP are dose normalized

In the groups not receiving hydrocortisone the concentrations of exogenous AVP with the higher and lower infusion rate were comparable 24 h and 48 h into the infusions, respectively, indicating dose proportional PK for AVP in the patients not receiving hydrocortisone.

In the groups receiving hydrocortisone the plasma concentrations of AVP 24 and 48 h into the infusions were 1.6 and 1.5 fold greater, respectively, with the 0.067 U/min infusion rate than with the 0.033U/min infusion rate. This finding suggests a greater impact of hydrocortisone on the exposure to AVP when AVP is infused at the higher rate.

AVP Infusion Rate	Ratio of Plasma Concentrations of AVP in Group Receiving Hydrocortisone to Plasma Concentration of AVP in Group not Receiving AVP	
U/min	24 h	48 h
0.033	1.1	0.83
0.067	1.6	1.2

The plasma concentrations of AVP in the group receiving hydrocortisone and in the group not receiving hydrocortisone 24 and 48 h into the infusions are comparable when AVP is infused at a rate of 0.033 U/min. However, when AVP is infused at the higher rate the exposure to AVP is greater in the group receiving hydrocortisone than in the group not receiving hydrocortisone. This finding suggests that hydrocortisone tends to impact the exposure to AVP only during the higher infusion rate. The possible interference of hydrocortisone with the assay of AVP appears not to have been tested. However, an assay related interference as an explanation is not very persuasive given the interaction is only observed when AVP is infused at the higher rate. There is no obvious mechanistic explanation for the interaction by hydrocortisone.

The prolactin levels tended to increase comparably during infusions with the higher and lower infusion rates of AVP.

PD

The demographic and clinical characteristics of the subjects are listed in the below table:

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The effects of vasopressin infused at constant rates of 0.033 and 0.067 U/min on the hemodynamic organ function variables are listed in the below tables:

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The mean infusion rate at the 0.033 level was maintained over the entire 48 h period, whereas the mean 0.067 infusion rate decreased to 0.057 and 0.042 24 and 48 h after

initiation. The following significant differences over time between groups were observed: Heart rate and norepinephrine dose requirements decreased over time with both AVP treatments while MAP increased with both AVP infusion rates. The Patients on 0.067 U/min AVP required less NE compared to the patients on 0.03 U/min AVP. The AVP levels and NE requirements were indirectly correlated. Base deficit fell and arterial pH increased with both AVP treatments. Arterial lactate, and base deficit decreased while arterial pH increased during the infusion with either rate. Platelets fell in both AVP treatment groups, but the reduction over time was only significant at the 0.033 U/min level. Patient allocated to the 0.067 AVP infusion rate exhibited lower troponin T levels and base deficits than patients in the 0.033 U/min group. Simultaneous hydrocortisone therapy did not impact the hemodynamic response to AVP.
Safety
▪ Was there any death or serious adverse events? ☑Yes ☐ No ☐ NA ▪ The rate of adverse events during AVP infusion was comparable between groups
Conclusion
PK • The PK of AVP at infusion rates of 0.033 or 0.067 U/min are dose proportional • Co-administration of hydrocortisone increases the exposure to AVP 1.5-1.6 fold **PD** • Heart rate and NE dose requirements decreased with AVP given at a rate of 0.067 U/min, while MAP increased with both AVP infusion rates. Base deficit fell and arterial pH increased with both AVP treatments. Arterial lactate, troponin T levels and platelets fell only with the 0.033 U/min infusion rate. • Simultaneous hydrocortisone therapy did not impact the hemodynamic response to AVP • The rate of adverse events during AVP infusion was comparable between groups **Limitations of study** • Hemodynamic variables differ between the groups before randomization requiring correction when comparing the groups over time. Although this is an accepted statistical method it may affect negatively the comparison of the low and high infusion rate treatments with AVP. • Open-label study design.
Comments
• None

8.4

Report #	**Study Period:** Not indicated	**EDR Link**
Title	Vasopressin Decreases Intestinal Mucosal Perfusion: A Clinical Study on Cardiac Surgery Patients in Vasodilatory Shock. Nygren, A, Thoren A, Rickstein S-E. Acta	

Reference ID: 3313815

	Anesthesiol Scand 2009;53:581-588

Study Design: Single group study in 8 mechanically ventilated post-cardiotomy patients with vasodilatory shock receiving sequential 30 min infusions of ascending rates of vasopressin 0.02, 0.04 and 0.08 U/min. The simultaneous infusion rate of norepinephrine (NE) was modified to maintain a mean arterial blood pressure (MAP) of 75 mm Hg. A titration period of 5-15 min was needed for each infusion rate to obtain the target MAP. In the post-intervention period MAP was maintained at 75 mm Hg. The inotropic medication was not changed and additional fluids, except for replacing urine loss were not administered.

Rationale: Post-cardiotomy vasodilatory shock is characterized by a profound arteriolar vasodilation caused by endogenous vasodilators including nitric oxide, prostaglandins, inflammatory mediators or activation of the ATP sensitive potassium channels in vascular smooth muscle cells, promoted by e.g. lactic acidosis (1,2). Resistance to catecholamines via down regulation of adrenergic receptors may also contribute (3,4). Plasma levels of endogenous AVP are reportedly low in post-cardiotomy vasodilatory shock and in septic shock in contrast to hypovolemic and cardiogenic shock suggesting that this deficit contributes to the development of post-cardiotomy or septic shock (5,6). An increased sensitivity to AVP has been claimed as well (7). Concerns regarding a reduction of splanchnic perfusion and increases in transaminases and total bilirubin in vasodilatory shock have been raised (8,9). To gain more insight of AVP's effect on local gastric and jejunal perfusion ascending doses of vasopressin were infused into patients with post-cardiotomy vasodilatory shock.

Objectives: Primary: To study the dose-exposure and response profile of ascending doses of vasopressin

Endpoints: Mean arterial blood pressure, heart rate (HR), cardiac index (CI), central venous pressure (CVP), pulmonary artery occlusion pressure (PAOD), systemic vascular resistance index (SVRI), stroke volume index (SVI), systemic oxygen delivery index (DO_2I), systemic oxygen consumption (VO_2I), systemic oxygen extraction (SO_2 extr), mixed venous oxygen saturation (SVO_2), hemoglobin

Inclusion Criteria: Mechanically ventilated patients with post-cardiotomy vasodilatory shock who fulfilled the following criteria: MAP < 60 mm Hg despite optimal pre-load as assessed by right- and left sided cardiac filling pressures and transesophageal echocardiography, need for norepinephrine to obtain MAP> 60 mm Hg, CI > 2.5 L/min/m^2

Exclusion Criteria: Not indicated

Screening: Not indicated	**Washout:** not applicable
Periods	Not applicable

Treatment: Sequential intravenous infusions of 0.02, 0.04, 0.08 U/min vasopressin

Sequence	Not applicable

Dose Selection: 0.02, 0.04 and 0.08 U/min AVP are doses previously shown to exert pharmacological effects

Investigational Drugs and Formulations: Identity and source of the vasopressin infused were not indicated by the publication. However, upon inquiry the authors indicate that Pitressin (Parke-Davis) was administered to the patients

Administration: Constant rate intravenous infusion of vasopressin for 30 min at each dose

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level

Fed/Fasted: Not indicated

Interfering Substances: milrinone, dopamine, NE for blood pressure support, fentanyl, midazolam for sedation

PK and PD Sampling Times: Plasma samples of vasopressin were measured at baseline and at the end of each 30 min infusion period and 30 min after stopping the highest infusion rate. Body temperature, MAP, CVP, PAOP, and HR were continuously measured.

Analytical Method

The method used for the determination of vasopressin in serum was not indicated in the publication. However, after inquiry the authors indicate that AVP was extracted in plasma with cold ethanol. The coefficient of variations for intra- and inter-assay variability were <10% and <16%, respectively.

Analyte		Vasopressin
Method		Not indicated
Matrix		Serum
Range, ng/mL		Not indicated
Quality Control	%CV	Not indicated
	%RE	Not indicated

Lactate

The lactate concentrations were measured by an enzymatic method.

PD Methods

Jejunal mucosal perfusion was measured by laser Doppler flowmetry and gastric mucosal pCO2 by tomometry. The hepatic vein was catheterized. Blood gas analyses were performed using an automated blood gas analyzer.

Target PK Parameters: $C_{baseline}$, $C_{30\ during\ infusion}$, $C_{30\ after\ infusion}$

PK Data Analysis: t1/2 calculated from comparing $C_{30\ during\ infusion}$ with $C_{30\ after\ infusion}$

Target PD Parameters: MAP, HR, CI, CVP, PAOP, SVRI, SVI, DO_2I, VO_2I, SO_2 extr, SVO_2, hemoglobin

Statistical Method/Sample Size/Power: The Kolmogorov-Smirnov test for goodness of fit to a normal distribution was used and normality was obtained for all main measurements. ANOVA for repeated measurements and linear trend test were used to evaluate the effects of vasopressin on the measured variables. Pre- and post-infusion values were compared using a paired Student's t-test. Therefore the selected sample size was not based on power considerations.

Results

Study Population:

Randomized	8
Treated	8
Completed	8
Discontinued	0
Pharmacokinetic population	8
Safety population	8
Age [Mean (SD)], years	70(7)
Weight [Mean (SD)], kg	Not indicated

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Male/Female	7/1
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated

The clinical characteristics of the patients at study entry are summarized in the below table:

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The interval between cardiotomy and study entry ranged widely between 2 and 19 days. The SOFA scores were in all patients ≥ 9 and all patients suffered from multiple organ failure. Three (3) patients had an identified source of infection (pneumonia or urosepsis). The 5 patients without infection were considered to have post-cardiotomy vasodilatory shock. Four patients received dopamine and 4 patients received intravenous milrinone. All but one patient left the ICU alive. The one patient died of multiple organ failure 10 days after the study.

The mean (SD) serum concentration of vasopressin and associated changes in the pharmacological endpoints are summarized in the below table:

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PK

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The mean (SD) endogenous AVP concentration at baseline was 3.1(1.8) pg/mL. The baseline uncorrected mean serum concentrations 30 min after initiation of the infusions calculated by the Reviewer are listed in the below table:

Dose Normalized Mean Concentrations and Clearances of AVP

Infusion Rate, U/min	C_{30}, pg/mL	C_{30}Dose Normalized	Clearance, mL/min
0.02	24.0 (7.7)	24.0	1542
0.04	42.8 (12.8)	21.9	1723
0.08	89.0 (23.0)	23.0	1663

The dose normalized C_{30} after infusion rates between 0.02 and 0.08 U/min were constant indicating apparent linear PK of AVP in the patients.

PD

The doses of NE required to maintain MAP > 75 mm Hg during the 3 vasopressin infusions could be significantly reduced. The incremental doses of vasopressin were accompanied by a significant decrease in CI, SVI, DO_2I, and SVO_2. The changes in these parameters tended to increase with the increase in the infusion rate of AVP. The effect of NE on splanchnic perfusion is reportedly negligible (10). Thus, the changes in the splanchnic perfusion observed in this study are attributable to vasopressin.

Splanchnic Perfusion

The effects of the incremental doses of vasopressin on the splanchnic perfusion are shown in the below table and figure:

Increasing doses of vasopressin decreased jejunal mucosal perfusion and increased the arterial-gastric mucosal pCO2 gradient. In contrast, the hepatic blood gas analyses and lactate concentration were not impacted by vasopressin. Pre-and post intervention values of the various splanchnic variables did not differ significantly.

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
-

Conclusion

PK

- The PK of AVP is dose proportional at rates between 0.02 and 0.08 U/min
- The estimated CL ranges between 1542 and 1723

PD

- Increasing doses of AVP decreased jejunal mucosal perfusion and increased the arterial-gastric mucosal pCO2 gradient

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Limitations of the study include:

- The interval between cardiotomy and study entry varies significantly among the patients. This may have affected the response to vasopressin
- The protocol prescribed titration of NE to a MAP > 75 mm during the infusions with the incremental doses of vasopressin Hg made it impossible to evaluate the exposure-response relationship of vasopressin.

Comments

- None

References

11. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock N Engl J Med2001;345:588-595
12. Parillo JE. Pathogenic mechanisms of septic shock N Engl J Med 1993;328:1471-1477
13. Tsuneyoshi I, Kanmura Y, Yoshimura N. Nitric oxide as a mediator of reduced arterial responsiveness in septic patients Crit Care Med 1996;24:1083-1086
14. Meadows D, EdwardsJD, Wilkins RG, Nightingale P. Reversal of intractable septic chock with norepinephrine therapy. Crit Care Med 1988;16:663-666
15. Argenziano M, Chen JM, Choudhri, AF, Cullinane S, Garfein E, Weinberg AD, Smith Jr CR, Rose EA, Landry DW, Oz MC. Management of vasodilatory shock after cardiac surgery: Identification of predisposing factors and use of a novel pressor agnet. J Thorac Cardiovasc Surg 1998;116:973-980
16. Argenziano M, Choudri AF, Oz MC, Rose EA, Smith CR, Landry DW. A prospective randomized trial of arginine vasopressin in the treatment of vasodilatory shock after left ventricular assist device placement. Circulation 1997;96:II-286-290
17. Landry DW, Levin HR, Gallant EM, Seo S, D'Alessandro D Oz MC, Oliver JA. Vasopressin deficiency contributes to the vasodilation of septic shock [see comments] Circulation 1997;95:1122-1125
18. Duenser MW, Mayr AJ, Ulmer H, Ritsch N, Knotzer H, Pajk W, Luckner G, Mutz NJ, Hasibeder WR. The effects of vasopressin on systemic hemodynamics in catecholamine –resistant septic and post-cardiotomy shock: a retrospective analysis. Anaesthet Analg 2001;93:7-13
19. Luckner G, Duenser MW, Jochberger S, Mayr VD, Wenzel V, Ulmer H, Schmid S, Knotzer H, Pajk W, Hasibeder W, Mayr AJ, Friesenecker B. Arginine vasopressin in 316 patients with advanced vasodilatory shock. Crit Care Med 2005; 33:2659-2666
20. Nygren A, Thoren A, S-E Ricksten. Norepinephrine and intestinal mucosal perfusion in vasodilatory shock after cardiac surgery. Shock 2007;28:536-543

Reference ID: 3313815

8.5

Report #	Study Period: January 1999 - December 31, 2003	EDR Link
Title	Arginine Vasopressin in 316 Patients with Advanced Vasodilatory Shock. Luckner G, Duenser MW, Jochberger S, Mayr VD, Wenzel V, Ulmer H, Schmid S, Knotzer H, Pajk W, Hasibeder W, Mayr AJ, Friesenecker B. Crit Care Med 2005 33:2659-2666	

Study Design: Retrospective Study. Between January 1999 and December 2003 a cohort of 316 patients with advanced vasodilatory shock admitted to the 23 bed ICU of this tertiary teaching hospital and receiving supplemental vasopressin (AVP) has been analyzed. Patients were grouped into 1) Patients with septic shock 2) Patients with post-cardiotomy shock and 3) Patients with vasodilatory shock due to overwhelming systemic inflammatory response syndrome (SIRS). The syndromes of sepsis and SIRS were defined in accordance with to the American of Chest Physicians/Society of Critical Medicine Consensus Conference criteria. Age admission diagnoses, length of stay in ICU and AVP infusion, simplified Acute Physiology Score II, most severe multiple organ dysfunction syndrome score and ICU mortality were documented. All patients with vasodilatory shock were managed according to an institutional hemodynamic protocol with fluid resuscitation until the stroke volume (SV) could not be further increased. Central venous and arterial occlusion pressures were used to guide fluid resuscitation. If the SV remained < 25 mL/beat/m^2 or cardiac index (CI) was < 2.0 L/min/m^2, milrinone was started as a continuous infusion (0.3-0.7 µg/kg/min). An additional epinephrine infusion (0.05-0.3 µg/kg/min as administered only in patients with severe cardiac failure and who did not achieve a CI of > 2 L/min/m^2. If the mean arterial pressure (MAP) remained at < 70 mm Hg, a norepinephrine (NE) infusion was started. And in 218 of 316 patients a continuous hydrocortisone infusion (200-300 mg/day) was administered. If a stepwise increase of 0.2 µg/kg/min NE in 2 h did not restore MAP, AVP was started as a supplementary continuous infusion. The norepinephrine infusion rate was then adapted to maintain the MAP at > 70 mmHg. If the NE infusion could be decreased to < 0.3 µg/kg/min the AVP infusion was slowly tapered off in accordance with response of the blood pressure.

Rationale: Numerous reports indicate beneficial effects of AVP administration in vasodilatory shock. Concerns have been raised because of possible adverse events caused by AVP and lack of knowledge about the right time of initiating infusions with AVP.

Objectives: Primary: Study results provide information allowing clinicians to improve care of patients with vasodilatory shock

Endpoints: Heart rate (HR), MAP, central venous pressure (CVP), mean pulmonary arterial blood pressure (MPAP), CI, stroke volume index (SVI), and pulmonary artery occlusion pressure (PAOP) and cardiovascular drug dosage requirements.

Inclusion Criteria: Patients with septic shock 2) Patients with post-cardiotomy shock and 3) Patients with vasodilatory shock due to overwhelming systemic inflammatory response syndrome. The syndromes of sepsis and SIRS were defined in accordance with the American of Chest Physicians/Society of Critical Medicine Consensus Conference criteria.

Exclusion Criteria: Not stated

Screening: Not indicated	Washout: Not applicable

Reference ID: 3313815

Periods	Not applicable
Treatment: AVP at a rate of 0.067 U/min	
Sequence	Not applicable
Dose Selection: Previous studies suggest that AVP at an infusion rate of 0.067 is tolerated	
Investigational Drugs and Formulations: Synthetic AVP, Pitressin®, Pfizer, Karlsruhe, Germany. The publication does not state that AVP was dissolved in isosaline for infusion.	
Administration: Constant intravenous infusion of AVP	
Fed/Fasted: Not indicated	
Interfering Substances: Not indicated	
PK Sampling Times: No blood samples for AVP or the other administered drugs were collected	
PD Sampling Times: • Hemodynamic variables**:** Pre-dose, 0.5, 1, 4, 12, 24, 48, and 72 h after start of AVP infusion • Laboratory Variables: pre-dose, 24, 48 and 72 h after start of the AVP infusion	
Analytical Method: Not applicable	
Target PK Parameters: Not applicable	
PK Data Analysis: Not applicable	
Target PD Parameters • HR, MAP, CVP, MPAP, CI, SVI, PAOP and cardiovascular drug dosage requirements • pH, arterial lactate, serum creatinine, aspartate- and alanine aminotransferases, total bilirubin, $Pa0_2/FI0_2$ quotient, platelet count, phophocreatine kinase, troponin I • Adverse hemodynamic or laboratory events occurring during the AVP infusion	
Statistical Method/Sample Size/Power: Shapiro-Wilk's tests were used to check for normality of distribution of data, which was approximately fulfilled by all data with the exception of the values for aspartame- and alanine aminotransferases, total bilirubin, platelet count, arterial lactate, phosphocreatine kinase which were log transformed. The goal of the study is to provide preliminary information. The repeated measurements and differences between patients with septic, post-cardiotomy or SIRS related shock were analyzed with a mixed-effect model. If time effects were significant, comparisons vs. baseline were performed using the same model. Demographic, hemodynamic and laboratory and drug dosages before initiation of the AVP infusions were entered into a bivariate correlation model to test for univariate differences between patients with vs. patients without the observed adverse event. The differences in mortality between patients with vs without the adverse side effect were analyzed using the Fisher's exact test. Independent risk factors for death from advanced vasodilatory shock treated with AVP were analyzed using the same model. Because of its skewed distribution , the variable NE requirements before start of AVP therapy was grouped into three clinically relevant dosage steps 0-0.5, 0.5-1.0 and >1.0 µg/kg/min and then entered into the statistical model.	
Results	

Reference ID: 3313815

Study Population:

The below table lists demographics and baseline characteristic of the patients:

Treated Septic shock Postcardiotomy shock Shock due to overwhelming SIRS Safety population	316 103 135 78 316
Age [Mean (SD)], years	67(14)
Weight [Mean (SD)], kg	Not indicated
Male/Female	Not indicated
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated
Simplified Physiology Score II	46.7(15.2)
Multiple Organ Dysfunction Score	11.1(15.2) points equivalent to 5.6 failed organs
Mean Stay in ICU	17.8 (15.5) days
Mortality	50.9%
On continuous veno-venous hemofiltration (CVVHF)	79

Hemodynamic Responses to AVP

The below table lists the mean (SD hemodynamic variable at baseline and during the AVP infusions:

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HR, CVP and MPAP significantly decreased during the AVP infusion. In contrast, MAP, SVI, and SVR increased. Norepinephrine, milrinone, and epinephrine dosage requirements were significantly reduced during the 72 h observation period. There were no significant differences in the hemodynamic response to AVP in the patients with septic-, post-cardiotomy- or SIRS related shock. Changes in HR and MAP appear to occur as early as 0.5 h after initiation of the AVP infusions. However, because of the changes in the dosage of NE permitted per protocol

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an assessment of when the peak effect of AVP occurs is not possible.

Laboratory Responses to AVP

The next table lists the mean (SD) laboratory values at baseline and during the infusions with AVP:

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The pH, aspartate- and alanine aminotransferases and total bilirubin increased whereas arterial lactate concentrations and platelet count decreased. The observed increase in bilirubin and the decrease in platelet were due to the patients on CVVHF.

Safety

- Was there any death or serious adverse events? ☑Yes ☐ No ☐ NA

Adverse Event Responses to AVP

Table 3 presents the results of the statistical analysis:

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Significant changes included that CI decreased with no relationship to mortality, total bilirubin and serum transaminases increased and platelet count decreased.
Conclusions
• Relative to baseline HR, CVP and MPAP decreased and MAP, SVI, and SVR increased during the supplementary AVP infusions. • The co-administration of AVP reduced the dosage requirements for NE and milrinone. • pH, aspartate- and alanine aminotransferases and total bilirubin increased, whereas arterial lactate concentrations and platelet count decreased. The observed increase in bilirubin and the decrease in platelets were due to the patients on CVVHF. • Limitation: This a retrospective study, and the results must be interpreted with caution.
Comments
• None

9. PD in Patients on ACE Inhibitors Undergoing CPB

9.1

Report #	**Study Period:** April–October 2008	**EDR Link**

Reference ID: 3313815

Title	Prophylactic Vasopressin in Patients Receiving the Angiotensin-Converting Enzyme Inhibitor Ramipril Undergoing Coronary Artery Bypass Graft Surgery

Study Design: Prospective , randomized, double-blind, single center study. Forty-seven (47 patients on the ACE inhibitor ramipril for 6 weeks before undergoing elective primary cardiopulmonary bypass surgery. Patients were randomly divided into 3 groups: Group A (n=16) patients continued ramipril 24 h before surgery; Group B (n=16) patients continued ramipril until the morning of surgery; and Group C (n=15) patients continued ramipril until the morning of surgery and received AVP infusion (0.03 U/min)) from the onset of re-warming until the hemodynamics were stable without vasopressor agents. The anesthetic technique and conduct of CPB were standardized in the 3 groups. Hemodynamic parameters and vasoactive drugs were recorded for 3 days postoperatively. Standardized anesthesia was used with morphine 0.1 mg/kg and promethazine (0.5 mg/kg) intra-muscularly 1 h prior to induction of anesthesia. General anesthesia was introduced with fentanyl (3-5 µg/kg) midazolam (and rocuronium (0.9 mg/kg). Re-warming was started when at the time of re-anastomosing the last digital graft. Nitroglycerine infusion (0.5 µg/kg /min) was started at the onset of re-warming in all patients. After separation of the CPB, the administration of fentanyl 2 g/kg and pancuronium 2 mg was repeated. In the presence of a systolic arterial blood pressure (SAP) < 90 mm Hg , cardiac index ≤ 2.2 L/min/m2 and a systemic vascular resistance (SVR) > 600 dynes scm-5, dopamine (5-10 µg/kg/min, epinephrine (0.025-0.1 µg/kg/min), and intra-aortic balloon support were added sequentially. Postoperatively, all patients were shifted to the ICU. Dose requirements for the vasoactive drugs for the intra-operative and postoperative Days 0, 1 and 2 were calculated in terms of dose (µg/kg/min) x h for the whole group and then used to calculate the mean. Hemodynamic measurements were made before and after intubation, after sternotomy 5 min after termination of CPB, before shifting, on admission to the ICU, 1 and 2 h postoperatively and on postoperative days 1, 2 and 3.

Rationale: In patients with limited cardiovascular reserve such as after myocardial infarction and under the effect of anesthesia, pharmacologic rennin-angiotensin system blockade with ACE inhibitors is thought to precipitate unstable henodynamics. Correction of endogenous AVP deficiency by exogenous AVP could be the ideal prophylaxis for preventing post-CPB vasodilatory syndrome in patients receiving ACE inhibitor therapy.

Objectives: Primary: Mean arterial blood pressure (MAP) , heart rate (HR) , central venous pressure (CVP) , mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI) and systemic vascular resistance (SVR)

Endpoints:

Inclusion criteria: Patients undergoing elective CPB surgery on ramipril for > 6 weeks prior to surgery

Exclusion criteria: Patients with concomitant valvular disease, congestive heart failure, renal dysfunction (serum creatinine> 2.0 mg/dL, hepatic dysfunction, (serum bilirubin ≥ 3.0 mg/dL), peripheral vascular disease, stroke, hypersensitivity to AVP, undergoing emergency surgery or reoperation

Screening: Not indicated	**Washout:** Not applicable
Periods	Not applicable

Treatment: Group C received vasopressin and Groups A and received isosaline

Reference ID: 3313815

Sequence	Not applicable
Dose Selection: 0.03 U/min is considered a therapeutic dose in septic shock	
Investigational Drugs and Formulations:	
Administration: Intravenous infusion of 0.3 U/min	
Fed/Fasted: Overnight fasted	
Interfering Substances: β-blockers Calcium antagonists, statins, nitrates, potassium channel openers trimetazidine diuretics, dopamine, epinephrine, morphine, promethazine, midazolam, rocuronium, nitroglycerine, fentanyl	
PK Sampling Times: Not applicable	
PD Sampling Times: Hemodynamic measurements were made before and after intubation, after sternotomy, 5 min after termination of CPB, before shifting the patients to the ICU, on admission to the ICU, 1 and 2 h postoperatively and on postoperative days 1, 2 and 3.	
Analytical Method: No at applicable	
Target PK Parameters: Not applicable	
PK Data Analysis: Not applicable	
Target PD Parameters: MAP, HR , CVP , MPAP, PCWP, CI,SVR	
Statistical Method/Sample Size/Power: Qualitative data were analyzed using the χ2-test. Quantitative data were analyzed by analysis of variance or the Mann-Whitney U test. The hemodynamic variables recorded at various time intervals within the same group were compared with the baseline values using the paired t-test. The sample size of 47 subjects was calculated to a statistical power of 75% to detect a 20% decrease in MAP at a 0.05 level of significance.	
Results	

Reference ID: 3313815

Study Population:

Randomized		47
Treated		47
Completed		47
Discontinued		0
Pharmacokinetic population		0
Safety population		47
Age [Mean (SD)], years	Group A	56 (8.1)
	Group B	52 (11)
	Group C	59 (8.4)
Weight [Mean (SD)], kg	Group A	67 (8.5)
	Group B	69 (9.9)
	Group C	62 (10)
Male/Female	Group A	15/1
	Group B	16/0
	Group C	13/2
Race (Caucasian/Black/Hispanic/Asian/Other)		Not indicated

There was no significant difference in the demographics of the subjects in Groups A, B and C.

PK

The pre-operative characteristics of the patients are shown in the below table:

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The intra-operative variables of the patients are listed in the below table:

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Also, the intra-operative variables of the patients in the 3 groups were comparable

PD

The below figures show the time course of MAP and HR in the 3 groups of patients:

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Group A (stopped ramipril 24 h before surgery) exhibited stable MAP and SVR during the study period. Group A showed the smallest reduction of MAP during surgery. Group B (continued ramipril until the morning of the surgery) showed the greatest reduction in MAP. Group C receiving the same treatment of ramipril as Group B, but was infused with AVP at the time of re-warming showed a reduction of MAP greater than Group A but smaller than Group B which indicates that AVP neutralizes some of the hypotensive effects caused by ramipril and the surgical procedure. Group B exhibited a significant rise in HR during the post-operative period. In Groups B and C MAP and SVR were significantly less than in Group A.

The doses of vaso-active drugs, frequency and duration of their use in the 3 groups are listed in the below 2 tables:

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The patients in Group C used a significantly greater dose of nitroglycerine on post-operative Day 1. The patients of Group C were on dopamine and epinephrine for a significantly shorter time interval than the patients of Groups B. The same difference was present between Groups A and C, but the difference was not significant.
The patients of Group C required a higher dose of nitroglycerine on the first post-operative day compared to Groups A and B.

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Various transient arrhythmias were observed in all 3 groups. One patient in Group A developed cardiogenic shock (SAP < 90 mm Hg, PCWP >15 mm Hg and CI<2.3

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L/min/m2.
Conclusion
• Vasopressin 0.03 U/min reduces partly the reduction of MAP seen in patients on ramipril who take the drug until the morning of the CPB. • The patients on ramipril until the morning of the CPB and receiving AVP were on dopamine and epinephrine for a significantly shorter time interval than the patients on ramipril until the morning of the CPB not receiving AVP. • The results support the notion that AVP exhibits a pressor effect in the presence of ramipril and hypotension triggered by the anesthetic and surgical procedures involved in CPB.
Comments
• None

9.2

Report #	**Study Period**: Not indicated	**EDR Link**
Title	A Double-Blind, Randomized Trial: Prophylactic Vasopressin Reduces Hypotension after Cardiopulmonary Bypass. Morales DLS, Garrido MJ, Madigan JM, Helman DN, Faber J, Williams MR, Landry DW, Oz MC. Ann Thorac Surg 2003;75:926-930	
Study Design: Randomized, double-blind, placebo controlled, parallel group. The study drug infusion was started 20 min before initiation of CPB and maintained for a maximum of 72 h. The clinicians were allowed to administer any medication deemed clinically indicated, including open-label vasopressin if intractable shock developed. In this case the data from such subjects were segregated and reported separately.		
Rationale: Pre-operative use of ACE-inhibitors is known to be independently associated with an increased incidence of vasodilatory shock after cardiopulmonary bypass (CPB). Because vasopressin at low doses has little effect on blood pressure in healthy subjects, but becomes a potent pressor in vasodilatory shock the drug could be an ideal prophylactic agent for patients at risk.		
Objectives: Primary: To evaluate the effect of AVP on hemodynamic variables in patients treated pre-operatively with ACE inhibitors		
Endpoints: Incidence of hypotensive episodes (systolic blood pressure < 90 mm Hg for > 5 min), catecholamine requirements, and length of stay in ICU, peak dose of norepinephrine, duration of catecholamine (i.e. norepinephrine, phenylephrine or epinephrine), length of stay in ICU, AVP levels		
Inclusion Criteria: Patients undergoing CPB or valvular surgery were eligible for the study if they were ≥ 2 weeks pre-operatively on ACE inhibitors.		
Exclusion Criteria: Patients with hypovolemic or cardiogenic shock (cardiac index <1.8 L/m2 15 min after CPB were removed from the study		
Screening: Not indicated	**Washout:** Not applicable	
Periods	Not applicable	
Treatments: Vasopressin or saline		

Reference ID: 3313815

Sequence	Not applicable
Dose Selection: Infusion rates of up to 0.1 U/min AVP have been shown to be safe previously	
Investigational Drugs and Formulations: Solutions of vasopressin and normal saline. Identity and source of the vasopressin is not indicate in the publication	
Mode of Administration: Intravenous infusion of vasopressin 0.03 U/min or an equal volume of normal saline	
Fed/Fasted: Not indicated	
Interfering Substances: Except for ACE-inhibitors no other drugs specified	
PK Sampling Times: Pre-dose, 60 min on CPB, 90 min off CBP, and 90 min after completion of infusion.	
PD Sampling Times: Measurement of the hemodynamic variables was initiated 30 min prior to initiation of and then continued during the study drug infusions. Cardiac output was measured with a defined time point 15 min after completion of CPB to determine continued participation of the enrolled patients in the protocol.	
Analytical Method The publication does not provide information on the assay of vasopressin and its performance characteristics.	
Target PK Parameters: Vasopressin plasma concentrations before, during and after BCPB	
PK Data Analysis: Not applicable	
Target PD Parameters: Mean arterial blood pressure (MAP), cardiac index (CI), NE peak infusion rate, duration of catecholamine use	
Statistical Method/Sample Size/Power: All interval data were parametrically analyzed by the two-sample Student's t-test. Nominal data including sex distribution was analyzed by the Fisher exact test. Frequency data such as the number of hypotensive episodes was compared using Poisson regression techniques.Therefore the selected sample size is not based on power considerations.	
Results	
Study Population: The disposition of the patients in the trial is depicted in the below scheme:	

Reference ID: 3313815

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In 4 patients AVP had to be discontinued prematurely because e.g. central venous access was compromised. Two patients in the placebo group could not be weaned from vasopressors because of intractable vasodilatory shock and received vasopressin, which is the standard of care in the author' institution. Four (4) patients from the vasopressin group were disqualified when the study drug was inadvertently discontinued during the first 6 h, out of protocol. The responses of the remaining 27 patients were analyzed. Measurement of the hemodynamic variables at baseline was not performed in 5 first patients.

The baseline characteristics of the patients listed in the below table show comparability of the two treatment groups:

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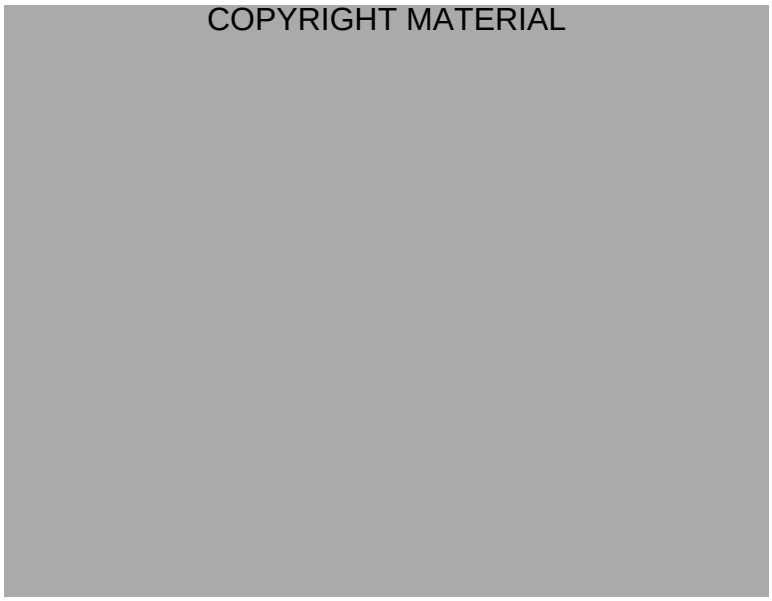
All patents took preoperatively ACE inhibitors, but the individual ACE-inhibitors taken by the patients in the two treatment groups were different. The type of cardiovascular procedure performed (CPB, valve procedures, combined re-vascularization and valve procedure) in the two treatment groups were also comparable.

Reference ID: 3313815

PK

The plasma concentration time profiles of AVP are shown in the below figure:



The pre-CPB plasma concentrations of AVP and the plasma concentrations of endogenous AVP 90 min after completion of the study drug infusions are comparable. However, during the infusions as expected the total (exogenous + endogenous) AVP concentrations exceeded the endogenous AVP concentrations. The AVP concentrations in the placebo group during the surgical procedures tended to be greater than prior to surgery.

PD

The impact of AVP on MAP, MPAP, peak NE dose requirements, number of hypotensive episodes and length of ICU stay are listed in the below 2 tables:

Mean (SD) Arterial Blood Pressure and Pulmonary Artery Pressure

	MAP	MPAP
	mm Hg	mm Hg
Before Vasopressin	80 (12)	22 (8)
During Vasopressin	78 (11)	23 (8)

Mean (SD) NE Dose Requirments, Number of Hypotensive Episodes, Duration of Catecholamine Use and ICU Stay

	Peak NE Dose	Hypotensive Episodes	Duration of Catecholamine Use	ICU Stay

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	μg/min	n	h	day
Vasopressin	4.6 (2.5)	1 (1)	5 (6)	1.2 (0.4)
Saline	7.3 (3.5)*	4 (2)*	11 (7)*	2.1 (1.4)*

* statistically significantly greater

Vasopressin treatment was associated with smaller peak NE doses, fewer hypotensive episodes, a shorter duration of catecholamine use and ICU stay than placebo.

The hemodynamic responses of the 6 enrolled patients who were excluded from the study are shown below:

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Two patients presenting with intractable septic shock despite a cardiac output > 5 L/min and NE > 8 μg/min exhibited an increase from 65 to 120 mm Hg and from 83 to 110 mmHg, respectively, within 15 min of the initiation of the open label AVP infusions. No episodes of hypotension were noted after discontinuation of AVP.
In 4 patients randomized to vasopressin AVP had to be discontinued prematurely during the first 6 h of treatment initiation because of loss of central venous access. Hypotension followed the premature discontinuation of vasopressin.

Safety

- Was there any death or serious adverse events? ☑ Yes ☐ No ☐ NA
- One patient in the vasopressin group developed acute renal insufficiency and right heart failure and one patient in the placebo group developed acute renal failure.

Conclusion

- Prophylactic vasopressin treatment in patients undergoing cardiotomy, who were pre-operatively on ACE-inhibitors, was associated with smaller peak NE doses, fewer hypotensive episodes, a shorter duration of catecholamine use and ICU stay than placebo.
- One patient in the vasopressin group developed acute renal impairment and right

Reference ID: 3313815

heart failure, one patient in the saline group exhibited acute renal failure
Comments
• None

9.3

Report #	Study Period: January 2003 –December 2005	**EDR Link**
Title	Perioperative Infusion of Low Dose of Vasopressin for Prvention and Management of Vasodilatory Vasoplegic Syndrome in Patients Undergoing Coronary Artery Bypass Grafting-A Double-Blind, Randomized Study. Papadopoulos G, Sintou E, Siminelakis S, Koletsis E, Baikoussis NG, Apostolakis E. J Cardiothorac Surg 2010;5: 1-12	
Study Design: Randomized, double blind, placebo controlled, parallel group, patients undergoing undergoing elective cardiopulmonary bypass (CPB) surgery because of chronic coronary artery disease. Induction of anesthesia used remifentanyl infusion at 0.5 µg/kg/min, intravenous etomidate at a titrated dose of 0.2-0.3 mg/kg and 0.6 mg/kg rocuronium and maintenance of anesthesia with remifentanyl at 0.25-0.50 µg/kg/min, sevoflurane, 1-2% and rocuronium at a rate of 20 mg/h. Systemic hypothermia (30°C), intermittent cold blood cardioplegia were used throughout the procedure. The study drug infusions started 20 min before beginning cardiopulmonary bypass and continued throughout the CPB procedure for 4 h. A nurse prepared the infusion solutions. The entire surgical team was blinded. The same anesthetic and surgical team performed the CPB surgery. Postoperative urine output and blood loss were recorded for the first 24 h. Ten (10) min before completion of surgery an infusion of norepinephrine (NE) 0.03 µg/kg/min was routinely administered and dependent on the hemodynamic condition was titrated up to 0.05 µg/kg/min during the next 24 h until extubation. All patients were sedated for the first 12-28 h then extubated in the absence of any hemodynamic instability. Sedation was maintained by a constant infusion of propofol 40 mg/h. until time of extubation. The hemodynamic profile was recorded at the following times: 20 min prior to initiation of extracorporeal circulation, 20, 40 and 60 min after termination of CPB and 120 min after transfer of patient to ICU. Postoperative urine output and blood loss were evaluated hourly for the first 24 h.	
Rationale: The incidence of post-cardiotomy hypotension is significantly increased with preoperative severe left ventricular dysfunction		
Objectives: Primary: Effects of prophylactic administration of low dose 0.03 IU/min vasopressin for 4 h on hemodynamic status, incidence of vasodilatory shock, and on urine output and blood loss for the first day after surgery.		
Endpoints: Ejection fraction (EF), heart rate (HR), mean arterial pressure (MAP), Mean pulmonary arterial pressure (MPAP), cardiac output (CO), central venous pressure (CVP), systemic vascular resistance (SVR) and peripheral vascular resistance (PVR), urine output and blood loss, dosage requirements for inotropes and NE		
Inclusion Criteria: On ACE inhibitor therapy for ≥ 4 weeks, left ventricular ejection fraction (EF) reduced to 30-40% of normal		
Exclusion Criteria: EF reduced to < 30%, in shock or critical hemodynamic state, confirmed hepatic, and/or renal, and/or thyroid and/or adrenal disease		

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Significant carotid stenosis or any event of intra-operative brain ischemia, documented significant chronic obstructive arteriopathy, documented systolic pulmonary hypertension(>30-35 mm Hg)		
Screening: Not indicated		**Washout:** Not applicable
Periods	Not applicable	
Treatments: Constant intravenous infusion of 0.03 U/min AVP or normal saline		
Sequence	Not applicable	
Dose Selection: Previous studies have shown that AVP infused at a rate of 0.03 U/min appears to exert pressor effects and to be safe		
Investigational Drugs and Formulations: AVP Pitressin® Pfizer, Karsruhe, Germany)		
Administration: Intravenous infusions of AVP or normal saline		
Fed/Fasted: Not indicated		
Interfering Substances: Except for ACE inhibitors no other drugs specified. However, the ACE inhibitors administered to the patients and their dose regimens were not indicated in the publication.		
PK Sampling Times: Blood samples for the determination of plasma concentrations of AVP were not collected		
PD Sampling Times: 20 min prior to initiation of extracorporeal circulation, 20, 40 and 60 min after termination of CPB and 120 min after transfer of patient to ICU. Postoperative urine output and blood loss were evaluated hourly for the first 24 h.		
Analytical Method: Not applicable		
Target PK Parameters: Not applicable		
PK Data Analysis: Not applicable		
Target PD Parameters: EF, HR, MAP, MPAP, CO, CVP, SVR, PVR, urine output and blood loss, dosage requirements for inotropes and NE		
Statistical Method/Sample Size/Power: The values in both groups passed the Kolmogorov-Smirnof test for normality. Comparisons of continuous variables used the unpaired Student's t test. Comparison of categorical variables used the chi-square or Fisher's exact test where appropriate. The selected sample size was not based on power considerations.		
Results		

Reference ID: 3313815

Study Population:
Twenty-five (25) patients were randomized to receive the AVP and normal saline treatments.
The baseline characteristics of the enrolled patients and the intra-operative data for the two treatment groups are provided in the below 2 tables:

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The pre-operative and intra-operative characteristics of the patients receiving AVP or normal saline were comparable.

Reference ID: 3313815

PD

The postoperative characteristics of the patients are shown in the below table:

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No death occurred in the AVP Group, whereas 3 patients in the Placebo Group died. The patients on AVP exhibited significantly greater values of MAP, SVR, CVP, and EF than the patients on normal saline. In contrast, HR, MPAP, CI and PVR were not different among the AVP Group and the Placebo Group. The number of patients experiencing vasodilatory shock, needing NE, additional epinephrine, the dosage requirements for NE, the mean infusion time for catecholamine were significantly reduced in the patients receiving AVP relative to the patients receiving placebo. In addition, urine volume was increased and blood loss decreased resulting in a reduced need for RBC and platelet transfusions in the patients on AVP.

The effect of the AVP and placebo treatments on MAP, CI and CV over 5 time points, i.e. 20 min before initiation of extracorporeal circulation (1), 20 min, 40 min and 60 min (2,3,4) after completion of cardiotomy, and 2 h (5) after transfer of the patient in the ICU is shown in the below figures:

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The post-operative data indicated that MAP, CVP, SVR and EF in the AVP Group A were statistically significantly greater than in the Placebo Group. There was no evidence for tachyphylaxis of AVP's pressor effect.

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- No death occurred in the patients treated with AVP and 3 deaths occurred in the subjects on placebo because of multiple organ failures.

Conclusion

- Patients receiving ACE-inhibitors pre-operatively who were randomized to AVP exhibited significantly greater values of MAP, SVR, CVP, and EF than patients randomized to normal saline.
- The numbers of patients experiencing vasodilatory shock, needing NE and additional epinephrine, and the dosage requirements for NE, and the mean infusion time for catecholamine were significantly reduced in the patients receiving AVP relative to the patients receiving placebo.
- Urine volume was increased and blood loss decreased resulting in a reduced need for RBC and platelet transfusions in the patients on AVP
- Three deaths occurred in the placebo Group
- Overall the results suggest that AVP may prevent postoperative shock in patients undergoing cardiotomy who received preoperatively ACE inhibitors.

Comments

- None

Reference ID: 3313815

10. Endogenous AVP in Healthy Adults

10.1

Report #	**Study Period:** not indicated	**EDR Link**
Title	A simple and highly Sensitive Radioimmunoassay for 8-Arginine Vasopressin in Human Plasma Using Reversed–Phase C_{18} Silica Column. Sakurai H, Kurimoto F, Ohono H, Kanai A, Nomura K, Demura H, Shizume K. Folia Endocrinol 1985; 61:724-736. Publication in Japanese was translated by Y. Harigaya, Pharm D, Division IV, OCP	
Study Design: Determination of plasma concentrations of endogenous AVP in healthy subjects in sitting, supine or standing position, after water loading, after infusion of a hypertonic solution and after smoking and in patients with diabetes insipidus		
Rationale: Develop a RIA with improved sensitivity to evaluate the effect of changes in body position, water loading, infusion of a hypertonic sodium chloride solution, smoking in healthy subjects and patients with a dysfunction of the antidiuretic hormone.		
Objectives: Primary: Determination of endogenous AVP levels in healthy subjects under varying conditions and in patients with dysfunction of the antidiuretic hormone		
Screening: not indicated	**Washout:** Not applicable	
Periods:	Not applicable	
Treatment: Not applicable		
Sequence	Not applicable	
Dose Selection: Not applicable		
Investigational Drugs and Formulations: Not applicable		
Administration: Not applicable		
Fed/Fasted: Not indicated		
Interfering Substances: Not indicated		
PK Sampling Times: 30, 60 and 90 minutes after changing condition		
PD Sampling Times: Osmolality in plasma was measured before and 30, 60 and 90 min after changing the condition.		

Analytical Method

Analyte		AVP
Method		RIA
Matrix		Plasma
Range, pg/mL		0.8-8.0
Quality Control	%CV	Not indicated
	%RE	Not indicated

Reference ID: 3313815

After mixing with 0.1 n HCL 0.5 mL plasma was passed through a SEP-PAK C18 cartridge and extracted with methanol. The recovery of the extraction procedure was 95%. Standard curves ranging from 0.5 to 8.0 pg/mL were established. Known concentrations of AVP added to plasma showed a mean recovery of 87%. The intra- and inter-assay coefficients of variations for 3 pooled plasma samples ranged between 7.9-14% and 8.2 and 14%, respectively. The minimum detection limit was 0.05 pg/tube. The assay is equally sensitive to AVP and lysine vasopressin. However cross reactivity towards oxytocin, DDAVP, vasotocin and pressinoic acid is negligible. Plasma samples containing two different AVP concentrations were serially diluted 2 to 32 fold using 0.1 M phosphate buffer resulting in a proportional right shift of the corresponding curves. Sample stability was tested at -30 ˚C, 4 ˚C and room temperature for 1 month. At -30 ˚C AVP was stable. However, at 4 ˚C and at room temperature the AVP concentration was reduced by up to 32% and 45%, respectively, after 1 month.

Target PK Parameters: Endogenous AVP concentrations at steady-state

Target PD Parameters: Plasma osmolality

PK-PD Data Analysis: Relationship between plasma osmolality and endogenous AVP concentrations

Statistical Method/Sample Size/Power: Not indicated

Results

Steady-Sate Plasma Concentrations of Endogenous AVP

Range of Plasma Concentrations in Healthy Subjects

The mean plasma concentration of AVP in 65 male and female subjects was 1.3 (range 0.30-4.2 pg/mL) with no significant impact of sex.

Impact of Body Position

The impact of various body positions on the plasma concentrations of AVP in 6 healthy subjects are shown in the below table:

Mean(SD) plasma Concentrations of AVP in Various Body Positions

Body Position	Mean (SD) AVP Level
Standing for 60 min	2.4 (1.2)
Sitting for 30 min	2.0 (0.85
Supine for 30 min	0.97 (0.48)

Endogenous AVP attained a steady-state within 30 min in the different body positions.

Impact of Water Loading (20 mL/kg) and Body Position

The impact of water loading in subjects in various body positions is shown for 3 subjects in the below table:

Reference ID: 3313815

Hydration Status and Body Position	Mean (SD) AVP Level
Water Loading, Standing for 60 min	1.9 (1.0)
Water Loading, Standing for 90 min	0.42 (0.21)
Water Loading, Supine for 60 min	0.89 (0.41)
Water Loading , Supine for 90 min	0.40 (0.22)

Impact of Infusion of Hypertonic 2.5% NaCL Solution

Following loading with a hypertonic NaCL solution the plasma AVP concentration increased from 2.2 (0.08) to 3.6 (0.73) pg/mL in 6 subjects.

Impact of Smoking

Peak concentrations of AVP 6-200 fold greater than the base line values were attained within 5-10 min in 3 subjects after smoking 2 cigarettes.

Range of Plasma Concentrations in Patients with Diabetes Insipidus

The plasma concentrations of AVP in 16 patients with diabetes insipidus were < 0.30 pg/mL.

Plasma Concentrations of Endogenous AVP in Patients with SIADH

The plasma concentrations of endogenous AVP in 2 patients with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) were 7.1 and 13.4 pg/mL.

PK-PD

The below figure shows the existence of an apparent linear relationship between AVP and osmolality in plasma in healthy subjects before an after they were water loaded by the oral route or infused with hypertonic 2.5% NaCL solution.

Reference ID: 3313815

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Safety
▪ Was there any death or serious adverse events? ☐ Yes ☐ No ☑NA
Conclusion
• Sex does not impact the plasma concentration of endogenous AVP in healthy subjects. Body position, water loading, infusing a hypertonic NaCL solution, or smoking changes the level of endogenous AVP. The development of the full effect on endogenous AVP after water loading in the upright or supine position takes ≥ 90 min. Smoking appears to provoke the greatest increase in endogenous AVP in healthy subjects with a peak effect attained within 5 to 10 min. Thereafter the endogenous AVP concentrations decay. • The endogenous AVP levels in patients with central diabetes insipidus are negligible and those in patients with SIADH appear to be significantly increased.
Comments
• None

10.2

Report #	**Study Period:** Not indicated	**EDR Link**
Title	Radioimmunoassay of Arginine Vasopressin in Human Plasma and Urine, a Resin Column Method. Kimura T, Matsui K, Ota K, Yoshinaga K. Tohoku J Exp Med 1980;131: 37-46	
Study Design: Parallel group design study in healthy subjects, patients with diabetes insipidus or Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH) under variously states of hydration: a) Normal hydration: blood was collected from 30 healthy		

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subjects and 7 patients with SIADH 2 h after a meal in the ambulatory state. Urine samples were collected from 10 normal subjects, 9 patients with diabetes insipidus and 9 patients with SIADH for 24 h while ambulatory. All subjects were non-smoking b) Water deprivation: Blood was collected from 31 healthy subjects and a 1 h urine sample was collected in 14 healthy subjects after an overnight fast. Eleven (11) patients with diabetes insipidus were dehydrated to 97% of their body weight and blood samples collected c) Water loading: Blood was collected from 8 healthy subjects 1-2 h after an oral water load (20 mL/kg body weight). Urine samples were collected from 6 healthy subjects starting 1 h after the water load.

Rationale: The results on the plasma concentration of AVP measured by different reported radio-immunoassays are not consistent. To develop a sensitive and reliable radio-immunoassay (RIA) for AVP in plasma and urine.

Objectives: Primary: To measure AVP in plasma and urine by a newly developed sensitive and reliable RIA

Endpoints: Plasma and urine concentrations in blood and urine samples collected from healthy subjects, patients with diabetes and patients with SIADH

Screening: Not indicated	**Washout:** Not applicable
Periods	Not applicable

Treatment: Water deprivation, water ad lib, water loading

Sequence	Not applicable

Dose Selection: Not applicable

Investigational Drugs and Formulations: Not applicable

Administration: Not applicable

Fed/Fasted: Subjects in normal hydration state were fed. Subjects in water deprivation were fasted. Fasted/fed state of subjects undergoing water loading was not indicated

Interfering Substances: Except for smoking not indicated

PK Sampling Times: Plasma concentrations and urine excretion rates of endogenous AVP at steady-state

PD Sampling Times: Plasma osmolality was measured in plasma at the same time as the plasma concentration of endogenous AVP

Analytical Method

AVP

Analyte		AVP
Method		RIA
Matrix		Plasma
Range, ng/mL		Not indicated
Quality Control	%CV	Not indicated
	%RE	Not indicated

Osmolality

Osmolality was measured in plasma by an advanced osmometer

Target PK Parameters: steady-state plasma concentrations and urine excretion rates of AVP at steady-state in healthy subjects under normal conditions, water deprivation and water loading

PK Data Analysis: Rough estimates for the renal clearance of endogenous AVP were obtained by the Reviewer from CL_R=(dAe/dt)/Css, where dAe/dt is the mean excretion rate

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and Css is the mean plasma concentration of endogenous AVP at steady-state for the healthy subjects under normal and water deprived conditions. The publication reported mean Css and dAe/dt only for the healthy subjects under normal and water deprived conditions.

Target PD Parameters: Not applicable

Statistical Method: Not indicated
Sample Size/Power: The selected sample size is not based on power considerations.

Results

Study Population:

Baseline characteristics of the study subjects beyond what is described above under study design were not provided by the publication.

PK

The mean (SD) concentrations, excretion rates and renal clearances of endogenous AVP in ambulatory healthy subjects in varying states of hydration are listed in the below table:

	Hydration Status	**Css**	**dAe/dt**	**CL_R**
		pg/mL	pg/min	mL/min
Healthy subjects	Water ad lib	3.9 (0.3)	81.5 (41.2)	21
	Water deprivation	4.9 (0.6)	66.7 (41.7)	14
	Water load	0.4 (0.2)	17.0 (12.0)	Not indicated

Water loading reduces the plasma levels of endogenous AVP signiificantly. The estimated CL_R under water ad lib conditions of 21 mL/min for endogenous AVP is not incompatible with the mean CL_R reported for exogenous AVP in healthy subjects (1).

PD
No significant correlation existed between the concentrations of AVP and osmolality in the healthy subjects as shown below:

1. Moses AM, Steciak E. Urinary and metabolic clearances of arginine vasopressin in normal subjects. Am J Physiol 1986;251:R365-R370

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

- The estimated CL_R of endogenous AVP in healthy subjects under normal conditions is about 20 mL/min in accordance with estimate for the CL_R for exogenous AVP.

Comments

- None

10.3

Reference ID: 3313815

Report #	Study Period:	EDR Link:
Title	Serum Vasopressin Concentrations in Critically Ill Patients. Jochberger S, Mayr VD, Luckner G, Wenzel V, Ulmer H, Schmid S, Knotzer H, Pajk W, Hasibeder W, Friesenecker B, Mayr AJ, Duenser M. Crit Care Med 2006;34: 293-299	
Study Design: Prospective study examining the serum concentrations of endogenous AVP and other endpoints and demographic characteristics of critically ill adult patients 24 h after intensive care unit admission and comparing the results to those in healthy controls. Over a period of 11 months 239 patients mixed critically ill patients were investigated in a single study center. All patients were volume-resuscitated. If stroke volume remained <25 mL/min/m2 or echocardiography showed a decreased ejection fraction (<50%) despite adequate volume resuscitation milrinone and/or epinephrine infusion was started. In order to increase mean arterial blood pressure (MAP) > 70 mmHg phenylephrine infusion (mild cardiovascular failure) or norepinephrine infusion (moderate or severe cardiovascular failure) was continuously administered. Systemic inflammatory response syndrome and sepsis were defined in accordance with the guidelines of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM). For determining the normal range of AVP serum concentrations, 70 healthy subjects (blood donors) of mean (SD) age 40.5 (11.8) years were examined.		
Rationale: It is known that patients with septic shock exhibit significantly lower concentrations of AVP than patients with cardiogenic shock. It was hypothesized that substitution of AVP deficiency in septic shock may be beneficial. Adequate AVP concentrations in critically ill patients have not been determined. The purpose of this study is to do that. The 24 h time point for sampling was chosen to prevent inclusion of patients in acute still untreated shock states.		
Objectives: Primary: To determine what adequate concentrations of endogenous AVP constitute in critically ill patients and to search for a possible correlation between AVP concentrations and demographic, hemodynamic or clinical endpoints		
Screening: Not indicated	**Washout:** None	
Periods	1	
Treatment: Not applicable		
Sequence	Not applicable	
Dose Selection: Not applicable		
Investigational Drugs and Formulations: Not applicable		
Administration: Not applicable		
Fed/Fasted: not indicated		
Interfering Substances: None		
PK Sampling Times: In patients arterial blood for the determination of endogenous AVP was collected 24 h after admission to the emergency unit. Although not specified, venous blood was collected in the healthy controls**.**		
PD Sampling Times: Not applicable		

Reference ID: 3313815

Analytical Method

Analyte		VP
Method		RIA
Matrix		Serum
Range, ng/mL		Not indicated
Quality Control	%CV	Not indicated
	%RE	Not indicated

After collection of the blood samples were immediately centrifuged and frozen at -80°C. After thawing the samples were extracted with ethanol, evaporated and reconstituted in assay buffer. AVP was measured by RIA (DRG Diagnostics, Marburg, Germany) based on the method published by Beardwell et al). The calibration standard curve ranged between 0.5 and 60 pg/mL. The LOQ was 0.1 pg/mL. If results were significantly outside of the expected range (<0.83 pg/mL or > 50 pg/mL they were repeated and results were reconfirmed. The publication does not indicated the procedure used when the repeat value and the original value were at variance.

Target PK Parameters: Arterial serum concentration of AVP 24 h after admission to emergency unit in patients. Venous serum concentrations in blood donating healthy volunteers.

PK Data Analysis: None

Target PD Parameters: Not applicable

Statistical Methods/Sample Size/Power: The primary endpoint was to compare serum AVP concentrations in critically ill patients and in healthy subjects and to search for a possible correlation between AVP concentrations and demographic, hemodynamic and clinical parameters. The secondary endpoint was to compare AVP concentrations in patients with different admission diagnosis and shock states. The tertiary endpoint was to evaluate the incidence of absolute and relative AVP deficiency.
Kolmogorov-Smirnov tests were applied to check for normality of distribution. Approximate normality of distribution was found for the demographic, hemodynamic and clinical data, but not with the AVP concentrations which were log transformed. For determining whether correlations exist between hemodynamic, clinical or demographic variables and AVP concentrations bivariate linear regressions models were used. Student's t-tests were used to compare the AVP concentrations between patients and healthy subjects. Categorical data were compared with the chi-square test. Statistical significance was assumed if $p < 0.05$.

Results

Study Population

Critically ill patients	239
Sepsis	25
Cardiac surgery	96
Non cardiac surgery	67
Non-surgical	51
Pharmacokinetic population	239
Age [Mean (SD)], years	61 (15)
Weight [Mean (SD)], kg	Not indicated

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Male/Female	162/77
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated

Healthy Subjects Pharmacokinetic population	70 70
Age [Mean (SD)], years	41(12)
Weight [Mean (SD)], kg	Not indicated
Male/Female	Not indicated
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated

PK

The demographic, hemodynamic and clinical endpoints for the critically ill patients are listed in the below table:

Mean (SD) AVP Serum Concentrations in Healthy Subjects and in Critically Ill Patients[a]

	Mean(SD) AVP, pg/mL	Statically Significnat Difference p< 0.05
Healthy Subjects	0.92 (0.38)	
Patients	11.9 (20.6)	Healthy vs. Patients
Male	9.7 (19.5)	
Female	15.1 (20.6)	Male vs. Females
Hemodynamic Dysfunction	14.1 (26)	
No Hemodynamic Dysfunction	8.7 (10.8)	Hemodynamic Dysf. yes vs. no
Sepsis	6.5 (4.3)	
Cardiac Surgery	19.5 (30.4)	Cardiac Surgery vs. Noncardiac Surgery
Noncardiac Surgery	7.6 (6.5)	
Nonsurgical Procedures	6.5 (4.3)	Cardiac Surgery vs Nonsurgical Procedures
Septis	8.7 (4.3)	
Postcardiotomy	26.3 (39.5)	
SIRS*	8.1(9.4)	

[a] arterial concetration in patients, *SIRS=shock due to systemic inflammatory response syndrome

AVP concentrations were significantly related to male sex, admission diagnosis, incidemce ofhemodynamic function, and length of intensive care stay, but surprisingly not to the incidence of shock or other hemodynamic variables. This finding appears to suggest that endogenous AVP concentrations have no impact on cardiovascular function in critically ill patients. However, administration of exogenous vasopressin resulting in hgher concentrations of 150-250 pg/mL has been shown repeatedly to improve cardiovascular function.

Based on the results in healthy subjects and patients the authors defined an AVP value < 0.83 pg/mL to indicate an absolute AVP deficiency and AVP <10 pg/mL despite an MAP <70 mmHg to indicate relative AVP deficiency. The 10 pg/mL threshold was selected, because 10 pg/mL AVP was shown to induce an increase in vascular tone in the rat. Of the patients 15% exhibited an absolute (1.7%) or relative (13.4%) AVP deficiency. Patients with an absolute AVP deficiency had a significantly higher MAP and lower muliple organ

Reference ID: 3313815

dysfunction syndrome score than patients without AVP deficiency. Mean arterial blood pressure was significantly lower in patients with relative AVP deficiency than in subjects without AVP deficiency. There was no difference in the incidence of relative AVP deficiency between patients with different shock states. No patient with shock fulfilled the criteria for absolute AVP deficiency.
Safety
▪ Was there any death or serious adverse events? ☐ Yes ☐ No ☑ NA
Conclusions
• The mean concentrations of endogenous AVP are significantly greater in critically ill patients than in healthy subjects. AVP concentrations were significantly related to male sex, admission diagnosis, incidence of hemodynamic dysfunction, and length of intensive care stay, but surprisingly not to the incidence of shock or other hemodynamic variables. • The threshold of 0.83 pg/mL proposed by the authors for absolute AVP deficiency does not consider that the level of endogenous AVP depends on body position, hydration, and smoker status. The impact of these covariates was considered in the healty subjects investigated. The threshold proposed by the authors for relative AVP deficiency of 10 pg/mL is based on pressor effects of vasopressin determined in the rat not in humans. The authors should provide evidence in support of extrapolating from rat to man.
Comments
• None
References 1. Beardwell CG. Radioimmunoassay of arginine vasopressin in human plasma. J Clin Endocrin Metab 1971; 33:2554-260

11. Pediatrics

11.1

Report #	**Study Period:** August 2003-April 2007	**EDR Link**
Title	Vasopressin in Pediatric Vasodilatory Shock, A Multicenter Randomized Controlled Trial. Choong K, Bohn D, Fraser DD, Gaboury I, Hutchinson JS, Joffe AR, Litalien C, Menon K, McNamara P, Ward RE on behalf of the Canadian Critical Care Trials Group. AM J Resp Crit Care Med 2009;180:632-639	
Study Design: Multicenter, Randomized, Controlled Trial. Participants were randomized to receive either AVP or normal saline placebo, prepared in identical 50 mL syringes and infused at a starting dose of 0.0005U/kg/min. The study drug was administered in addition to the open-label vasoactive infusions that the patients were already receiving at baseline and titrated every 5 min up to 0.002U/kg/min (0.05 U/kg/min maximum total dose) to maintain a target mean arterial blood pressure (MAP) for age. Guidelines for the		

Reference ID: 3313815

management of ongoing hemodynamic instability and guidelines for the use of potentially confounding co-interventions such as steroids and activated protein C were established by consensus of the Steering Committee an participating investigators. Once the patient attained their target MAP for at least 4 h without escalation in hemodynamic support, accompanied by clinical evidence of adequate end-organ perfusion, open label vasoactive infusions were weaned in accordance with the guidelines. The study drug was weaned after both target MAP and end-organ perfusion were maintained without open-label infusion for at least 4 h. All patients, caregivers, medical and nursing staff, investigators, and members of the Data Safety Monitoring Committee were masked to the study group assignment for the duration of the study.	
Rationale: Adult trials before the start of this study suggested a beneficial effect of vasopressin in shock. In contrast, the evidence for its beneficial use in pediatrics is entirely observational. Children differ from adults regarding underlying disease processes, hemodynamic responses and oxygen utilization. Thus, shock management strategies are not necessarily the same in children and adults.	
Objectives: Primary: The trial in the pediatric population was conducted to test the hypothesis that low doses of vasopressin would be an effective adjunct in reversing vasodilatory shock in children.	
Endpoints: Primary: Time to vaso-active free hemodynamic stability defined as time from study drug initiation to the time when all vaso-active agents were successfully discontinued. Secondary**:** 30 day mortality, change in organ dysfunction as determined by the Pediatric Logistic Organ Dysfunction (PELOD) score and Multi Organ Dysfunction score (MODS), number of days alive and free of organ dysfunction (organ failure free days) vaso-active infusions (vaso-active free days) and mechanical ventilation (ventilation free days) in the 30 days after randomization, length of stay in the ICU, urine output and MAP after study drug administration. A modified vaso-active score was calculated to indicate the magnitude of vaso-active requirements. Vasopressin levels 4 h into infusions and rate of adverse events and serious adverse events.	
Inclusion Criteria: Patients aged 1 month to 17 years with indwelling arterial and ventral venous catheters if they were within 24 h of the diagnosis of vasodilatory shock [volume resuscitation of ≥ 40 mL/kg, ≥ 10 mg/kg/min dopamine or any dose of epinephrine, norepinephrine, or phenylephrine, and clinical evidence of vasodilatory shock (diastolic blood pressure half of systolic blood pressure and two of the following: tachycardia, warm extremities, or flash capillary refill)	
Exclusion Criteria: Death anticipated within 24 h or a lack of commitment to life support, use of vasopressin or its analogs in previous 24 h, known history of vaso-spastic diathesis, concurrent use of intravenous vasodilators, hypersensitivity to vasopressin serum sodium < 125 meq/L despite water restriction, known diagnosis of diabetes insipidus or syndrome of inappropriate anti-diuretic hormone secretion, pregnancy, low cardiac index (<2.5 L/min/m^2).	
Screening: Not indicated	**Washout:** Not applicable
Periods	Not applicable
Treatment: Infusions of arginine vasopressin or saline	
Sequence	Not applicable

Reference ID: 3313815

Dose Selection: Previous studies showed that the selected dose range of AVP is safe and pharmacologically active in the pediatric population

Investigational Drugs and Formulations: Identity and source of AVP is not indicated in the publication. However, upon inquiry the primary author Dr. Choong indicated by e-mail that AVP (Ferring) was used in the trial.

Administration: Intravenous

Fed/Fasted: Not indicated

Interfering Substances: Partly indicated

PK Sampling Times: Prior to starting the AVP infusion and 4 h into the AVP infusions

PD Sampling Times: Continuous monitoring

Analytical Method

Analyte		AVP
Method		RIA
Matrix		Plasma
Range, ng/mL		Not indicated
Quality Control	%CV	Not indicated
	%RE	Not indicated

Target PK Parameters: $C_{baseline}$ and C_{4h}

PK Data Analysis: Not applicable

Target PD Parameters: see Endpoints

Statistical Method/Sample Size/Power: The primary outcome was analyzed using a cause specific cumulative incidence because death could also be considered as a competitive risk. Continuous secondary variables were analyzed using the non-parametric Wilcoxon-Mann-Whitney test Fisher's exact test was used for dichotomous outcomes such as use of co-intervention drugs and indication for steroid use. Time to discharge form the ICU after study drug administration was compared using survival analysis. AE and SAE rates between groups were compared using a Poisson regression model. The tests were 2-sided. The sample size calculation used data from adult trials and anecdotal experience from Canadian pediatric intensivists. The calculations showed that 69 patients were required for enrollment to achieve 90% power to detect a hazard ratio of 3 and a significance level of 5% using Lakatos's formula for survival analysis study design. This sample size calculation accounted for a 34% mortality rate and a 7% drop-out or post-randomization exclusion rate.

Results

Reference ID: 3313815

Study Population:

Sixty-nine (69) patients were enrolled, 35 were randomized to receive AVP and 34 to receive placebo. Two (2) patients in each group were withdrawn shortly after randomization, but before initiation of any study procedures and without knowledge of group allocation. Three (3) of the patients no longer met the entry criteria and the fourth patient received open-label AVP infusion by the attending physician upon rapid progression of refractory shock. Three (3) additional patients, 2 belonging to the placebo group were withdrawn because of SAEs.

The below table shows that the baseline characteristics of the enrolled pediatric patients were comparable (median and interquartile range):

TABLE 1. BASELINE CHARACTERISTICS OF THE PATIENTS

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The below table lists the co-interventions for hemodynamic support during the Treatment Period (median and interquartile range):

TABLE 2. COINTERVENTIONS FOR HEMODYNAMIC SUPPORT DURING THE TREATMENT PERIOD

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The most common cause of vasodilatory shock was sepsis. The severity of the disease, the volume resuscitation and the open label vasoactive infusions were comparable in the two groups. The co-interventions between the groups were not different. The baseline concentrations of endogenous AVP were 3.8 pg/mL in both groups. The median infusion rate of exogenous AVP was 0.001U/kg/min [interquartile range (0.0007-0.0018)]. About 65% of the patients received corticosteroids for refractory shock.

PD

The study results are shown in the below table:

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There was no difference in the median time achieve hemodynamic stability. Also there was no difference among the groups regarding vaso-active-free, organ failure-free and ventilator free days, organ dysfunction scores and the length of stay in the ICU. MAP relative to baseline increased significantly more after AVP than placebo. There were 10 deaths in the AVP and 5 deaths in the placebo group. The most common cause of death was refractory shock. The mortality rate of patients with septic shock was 18.5% compared with a mortality rate of 33.3% for patients with vasodilatory shock from non-septic causes. The concurrent use of steroids and AVP was not associated with a statistically significant difference in mortality.

PK

The median (interquartile range) AVP concentration in the vasopressin receiving group was 99.2 (64.4-149.9) pg/mL 4 h into the infusions.

Safety

- Was there any death or serious adverse events? ☑ Yes ☐No ☐ NA

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- There was no difference between rates of AEs and SAEs between the AVP and placebo groups.

Conclusion

- There is no statistically significant difference in the primary outcome, time to achieve hemodynamic stability, between the treatments.
- There is no difference among the groups regarding vasoactive free, organ failure free and ventilator free days, organ dysfunction scores and length of stay in the ICU. There were 10 deaths in the AVP and 5 deaths in the placebo group.
- The rates of AEs and SAEs are not different between the treatment groups

Limitation of the study:

- No exploration of the dose/exposure-response relationship of AVP in the pediatric population

Reference ID: 3313815

Comments
• None

11.2

Report #	Study Period: March 2003- December 2005	EDR Link
Title	Arginine-Vasopressin in Neonates with Vasodilatory shock after Cardiopulmonary Bypass. Lechner E, Hofer A, Mair R, Moosbauer W, Sames-Dolzer E, Tulzer G. Eur Pediatr 2007;166:1221-1227	
Study Design: Retrospective study		
Rationale: Neonates undergoing cardiac surgery with long bypass duration are prone to experience post bypass systemic inflammatory response syndrome. There is limited data on the use of vasopressin (AVP) and indications and dosage have not been established. Data on the use of AVP in the treatment of vasodilatory shock after cardiac surgery were available in-house.		
Objectives: Primary: To review in-house data on the treatment of neonates with vasodilatory shock with AVP		
Endpoints: Systolic and diastolic arterial blood pressure (SBP and DBP), heart rate (HR), left atrial pressure, mean pulmonary artery pressure (MPAP), vasopressor requirements, urine output, serum lactate concentrations, sodium, creatinine, arterial gases, fluid requirements		
Inclusion Criteria: Systemic inflammatory response syndrome(SIRS) with hypotension resistant to traditional vasopressors, low cardiac output (CO)with hypotension (<55 mm Hg) refractory to fluid replacement and administration of high doses of dopamine, epinephrine, and norepinephrine (NE) with decreasing urine output and or increasing serum lactate levels, serum lactate, sodium, creatinine, arterial gases, fluid requirements		
Exclusion Criteria: Not indicated		
Screening: Not applicable	**Washout:** Not applicable	
Periods	Not applicable	
Treatment: Infusion with AVP		
Sequence	Not applicable	
Dose Selection: AVP starting dose range 0.00005-0.0002 U/kg/min up-titrated to 0.0001-0.001 U/kg/min to attain SBP > 65 mm Hg		
Investigational Drugs and Formulations: AVP Pitressin® (Parke-Davis) injection solution. Publication does not indicate that AVP was dissolved in isosaline for infusion.		
Administration: Intravenous infusion		
Fed/Fasted: Fasted		
Interfering Substances: Not indicated		
PK Sampling Times: Blood samples for the determination of the plasma concentrations of AVP were not collected.		
PD Sampling Times: The vasopressor score was measured prior to and 3 and 6 h after initiation of the AVP infusion. Serum sodium, lactate, creatinine and liver enzymes as well as arterial blood gases were regularly measured.		

Reference ID: 3313815

PD Data Analysis: The base line SBP was calculated as the average BP over 3 h prior to initiation of AVP or during time off bypass, if this was less < 3 h. Baseline SBP was compared to the SBP measured 1 h after the effective dose of AVP was attained. Fluid balance 12 h before and after AVP initiation was measured. Baseline urine output was measured over 6 h prior to and after initiation of AVP.

Analytical Method
Not applicable

Target PK Parameters: Not applicable

PK Data Analysis: Not applicable

Target PD Parameters: SBP, vasopressor score, lactate levels, urine output, fluid requirements, arterial oxygen saturation, serum sodium, creatinine and liver enzymes

Statistical Method/Sample Size/Power: Paired variables were analyzed by the Student paired t-test. The selected sample size was not based on power considerations.

Results

Seventeen (17) of 172 neonates undergoing cardiac surgery developed SIRS. None showed signs of systemic infection or myocardial dysfunction.

Study Population:

Treated Completed Discontinued Safety population	17 15 17 17
Age [Median, Range], days	6(3-12)
Weight [Median (Range)], kg	3.4 (2.0-3.9)
Male/Female	11/6
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated

The demographic and clinical characteristics as well the vasopressor scores and urine output before and 3, 6 h after initiation of the AVP infusion are listed in the below figure:

Reference ID: 3313815

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Four (4) patients had corrections of biventricular defects and 13 patients had correction of single ventricle defects. Sixteen (16) patients had ductal dependent lesions and received prostaglandins pre-operatively. The median bypass duration was 208 min (172-380 min). The AVP infusion was administered within median 16 (0-32) h in the operating room (n=1) or in the ICU (n=16). In 16 of 17 patients AVP was started at median 0.0001U/kg/min (range 0.00005-0.0002) and titrated up to a maximum median 0.0003 U/kg/min (0.0001-0.001). Due to a calculating error one patient received a starting dose of 0.001 U/kg/min, which was subsequently not up-titrated.

PD

Reference ID: 3313815

The infusion of AVP resulted in the following changes from baseline for SBP, vasopressor score, urine output, fluid requirements and arterial oxygen saturation:

Variable	Baseline	After AVP
SBP, mm Hg	49(8)	69(7)*
Vasopressor Score	30.9 (13)	11.4 (4.9)*[a]
Urine Output, cm^3/kg/h	1.33 (0.82)	2.17 (0.09)*[b]
Fluid Requirements, mL/kg/h	35 (10)	15 (10)*
Arterial oxygen saturation, %	67 (9.3)	76 (7.2)*

* statistically significant change from baseline a 6 h after AVP infusion,
[a] similar reduction is observed already 3 h into the AVP infusions [b] n=16

The lactate levels at baseline and 3 and 6 after AVP infusion did not show a consistent change, but the baseline concentration was significantly lower in the surviving patients. Serum sodium, creatinine and liver enzymes did not change during the first 24 h after initiation of AVP infusion.

Outcome
Thirteen (13) patients survived to discharge and 4 patients died (all after stage one palliation for single ventricle circulation). In 2 of these patients death was not related to AVP infusion, as the patients deceased due to additional complications 6 days after AVP was discontinued. In 2 patients death occurred during AVP infusion.

Safety

- Was there any death or serious adverse events? ☑Yes ☐ No ☐ NA
- In none of the patients were there clinical signs of peripheral ischemia or reduced organ perfusion observed throughout continuous infusion of AVP.

Conclusion

- Relative to baseline AVP infusion raises SBP, urine output, and arterial oxygen saturation and reduces vasopressor score and fluid requirements
- Limitation: Retrospective study in a small number of neonates

Comments

- None

11.3

Report #	Study Period: Feb 1997- April 1998	**EDR Link**
Title	Intravenous Arginine-Vasopressin in Children with Vasodilatory Shock after Cardiac Surgery. Berman Rosenzweig E, Starc TJ, Chen JM, Cullinane S, Timchchak DM, Gersony WM, Landry DW, Galantowicz, ME. Circulation 1999; 100:II-182-II-186	
Study Design: Retrospective study of 11 children treated within 48 h of cardiac surgery in the operating room or in the ICU of the Babies and Children Hospital of New York.		

Reference ID: 3313815

Rationale: A randomized trial in adult patients undergoing left ventricular assist device placement (LVAD) receiving AVP demonstrated a marked pressor response and a significant reduction in the need of norepinephrine (NE) dosage requirements. These findings prompted the use of AVP in a similar group of critically ill children.

Objectives: Primary: To evaluate the findings with AVP infusions in children in vasodilatory shock after cardiac surgery.

Endpoints: Systolic and diastolic blood pressure (SBP, DBP), heart rate (HR), right atrial pressure, left ventricular function (echocardiographic qualitative grading: normal, mildly or severely depressed), modified inotrope score originally described by Wernowsky (1) (dosages of dopamine + dobutamine + epinephrine •100 + milrinone •10), urine output, serum bicarbonate score, serum sodium

Inclusion Criteria: Hypotension refractory to multiple adjustments in standard cardiopressor therapy. Because efficacy and safety of AVP in children has not been determined AVP was initiated only in children with the most extreme refractory vasodilator shock considered to be near death despite use of conventional vasoactive compounds.

Exclusion Criteria: Not indicated

Screening: Not indicated | **Washout:** Not applicable

Periods Not applicable

Treatment: Intravenous infusion with AVP

Sequence Not applicable

Dose Selection: Based on the patients weight ranging between 0.0003 -0.002U/min

Investigational Drugs and Formulations: AVP Pitressin ® (Parke-Davis)

Administration: Constant intravenous infusion, titrated to effect (increase in BP without side effects)

Fed/Fasted: Fasted

Interfering Substances: Not indicated

PK Sampling Times: Pre-dose

PD Sampling Times: Pre-dose and after initiation of AVP infusion

Analytical Method

Analyte		AVP
Method		RIA
Matrix		Plasma
Range, ng/mL		Not indicated
Quality Control	%CV	Not indicated
	%RE	Not indicated

The publications indicate that the plasma concentrations of AVP were measured by the RIA of SmithKline Beecham.

Target PK Parameters: Plasma concentrations of endogenous AVP at baseline

PK Data Analysis: Not applicable

Target PD Parameters: Hemodynamic variables**:** SBP, DBP, HR, right atrial pressure, left ventricular function,
Organ perfusion variables: urine output, serum bicarbonate score, serum sodium

PD Data Analysis: Baseline BP was the mean BP measured over 8 h before AVP or

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during time off CPB if this time was < 8 h. The baseline urine output was calculated as the mean output over 8 h before initiation of the AVP infusion and compared to the average urine output calculated over 24 h after initiation of AVP. The serum bicarbonate score was calculated over period of 8 h to obtain the baseline and the score after initiation of the AVP infusion. The serum sodium was calculated as the mean over 24 h prior to and after administration of AVP.

Statistical Method/Sample Size/Power: Paired variables were analyzed by the paired t-test or the paired sign test when appropriate. T he selected sample size is not based on power considerations.

Results

Eleven patients met the inclusion criteria. Five (5) patients received the treatment in the operating room and 6 in the ICU. Nine (9) patients had vasodilatory shock and 2 patients cardiogenic shock

Study Population:

Treated Pharmacodynamic population Safety population	11 11 11
Age [Range] , days/months/years	3 days- 15 y
Weight [Mean (SD)], kg	Not indicated
Male/Female	5/6
Race (Caucasian/Black/Hispanic/ Asian/Other)	Not indicated

The demographic, clinical and baseline treatment characteristics of the patients are shown in the below table:

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PD

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The below table summarizes the qualitative evaluation of the left ventricle function at baseline, the impact of AVP on SBP, DBP and MAP and the outcome after 2 weeks:

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Cardiac function was severely depressed in 2 subjects mildly impaired in 2 subjects and considered normal in the remainder 7 subjects.

The treatment with AVP increased SBP, DBP and MAP consistently in all 11 children.

The below table summarizes the results of the impact of AVP and other target endpoints:

Impact of the AVP Infusions on Mean (SD) Target PD Endpoints

Endpoint	Baseline	During AVP Infusion[a]
SBP , mmHg	65(14	87(17)*
DBP, mmHg	35(11)	46 (13)*
MAP, mm Hg	45(11)	59 (11)*
HR, bpm	154(41)[b]	157(33)[b]
Right atrial pressure, mm Hg	11(6)[c]	11(6)[c]
Total inotrope score	43	23 [d]*
Urine Output, cm^3 /kg/h	3.9(3.0)	4.3(3.1)
Bicarbonate score	24(3)	23(2)
Serum sodium, mEq/L	141(7)[b]	138(7)[b]

* statistically significant [a] 1 h after initiation of infusion [b] n=10
[c] n=7 [d] measured 1 h after initiation of AVP

AVP increased significantly BP without impacting heart rate or right atrial pressure AVP also reduced the dosage of inotropes significantly.

Early Outcome (<14 days after initiation of AVP)
The 2 patients with cardiogenic shock died 6 h and 6 days after initiation of the AVP infusions, despite transient improvements in systemic BP. Of the 9 patients with vasodilatory shock 1 was taken off LVAD and subsequently underwent successfully heart transplantation, 1 avoided LVAD placement as a bridge to heart transplantation and 5 patients were successfully weaned from CPB.

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Late Outcome (≥14 days after initiation of AVP)
Eight (8) of the 9 early survivors were discharged from the hospital, 1 subjects remains hospitalized for chronic lung disease. Three (3) patients died within 14 days to 6 months after AVP administration for causes unrelated to the initial event: 1 patient died during an interventional cardiac catheterization, a second patient died during heart transplantation and a third patients died 6 months after heart transplantation, presumably from acute rejection.

PK
The pre-dose plasma concentrations of AVP were available only for 3 of the patients. The median concentration of AVP was 4.4 pg/mL.

Safety

- Was there any death or serious adverse events? ☑ Yes ☐No ☐ NA
- There was no episode of peripheral vasoconstriction or cyanosis requiring discontinuation of AVP

Limitations of study:

- Retrospective design

Conclusion

- AVP increases MAP and reduces the dosage of inotropes significantly.
- These changes occured consistently in all 11 patients tested.
- Despite transient improvement in MAP 2 patients with severely depressed left ventricular function died.
- Eight (8) of the 9 patients with vasodilatory shock were discharged form the hospital. One patient remained hospitalized because of chronic lung disease.
- No vasoconstriction or cyanosis is observed

Comments

- None

Reference
1. Wernowsky G, Wypij D, Jonas RA, Mayer JE Jr, Hanley FL, Hickey PR, Walsh AZ, Chang AC, Castaneda AR, Newburger JW, Wessel DL. Postoperative Course and Hemodynamic Profile of Arterial Switch of Operation in Neonates and Infants: AA Comparison of Low-Flow Cardiopulmonary Bypass and Circulatory Arrest. Circulation 1995; 92:226-2235

11.4

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Report #	Study Period February 2004 and November 2005	EDR Link
Title	Arginine-Vasopressin in Catechoalmine-Refractory Septic versus Non-Septic Shock in Extremely Low Birth Weight (ELBW) Infants with Acute Renal Injury. Meyer S, Gotschling S, Baghai A, Wurm D, Gortner L. Clinical Care 2006; 10: R71	

Study Design: Prospective assessment of AVP in 3 ELBW infants with catecholamine-refractory septic shock and acute renal injury [mean birth weight 600 (30) g] and 3 ELBW infants with non-septic shock and acute renal injury [mean birth weight 770 (1100 g)

Rationale: No data on the effect of AVP on preterm infants are available. However, in animals V_1 receptor mediated vasoconstriction contributes to renal and cardiovascular responses to exogenous AVP in utero in the last third of gestation. Sepsis and septic shock were based on the Society of Critical Care Medicine consensus conference of 1992 and its revised version published in 2003 with modification for normal values in neonates. Non-septic shock was defined as cardio-circulatory failure with concomitant organ failure (renal injury, hyperlactatemia) without an infectious etiology. Low cardiac output was defined as a shortening fraction of ≤ 25%. Acute renal injury was based on the RIFLE classification, and included two criteria: glomerular filtration rate (two fold increase in serum creatinine or urine output < 0.5 mL/kg/h for ≥ 6 h). Furosemide (0.5-2 mg/kg/h) was administered. The AVP infusion was started in the infants presenting with catecholamine resistant hypotension coupled with acute renal injury and hyperlactatemia. The target dose of AVP was 0.002 U/min. The dose of AVP was adjusted in accordance with the clinical course and included AVP bolus if MAP < 20 mm Hg. After restoration of MAP and urine output attempts were made to taper off AVP.

Objectives: Primary: To evaluate AVP as a rescue therapy in ELBW infants with septic shock and non-septic shock

Endpoints: MAP, heart rate (HR), urine output, serum lactate levels

Inclusion: Infants with catecholamine refractory hypotension caused by sepsis and by other etiologies (low cardiac output failure, circulatory collapse) not responding to prior fluid resuscitation, hydrocortisone therapy and high dose catecholamine infusion

Exclusion: Genetic disorders, malformations and diseases incompatible with life and birth weight > 1000 g

Screening: Not stated	Washout: Not applicable

Periods	No applicable

Treatment: Single intravenous infusions of AVP

Sequence	Not applicable

Dose Selection: Body weight normalized, target 0.002 U/min

Investigational Drugs and Formulations: Identity and manufacturer of AVP infused are not stated. The publication does not state that AVP was dissolved in isosaline for infusion.

Administration: Intravenous infusion

Fed/Fasted: Not stated

Interfering Substances: Catecholamines and hydrocortisone stated

PK Sampling Times: Blood samples for determining AVP plasma concentrations were not collected

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PD Sampling Times: Baseline, 2, 4, 8, 12 and 24 h after initiation of AVP infusions
Analytical Method: Not applicable
Target PK Parameters: Not applicable
PK Data Analysis: Not applicable
Target PD Parameters: MAP, HR, urine output, serum lactate
Statistical Method: Sample Size/Power: The goal of the study is to provide preliminary information. Therefore the selected sample size is not based on power considerations.
Results

Study Population:

Septic shock		
Treated		3
Completed		2
Discontinued		1
PD population		3
Safety population		3
Non-septic shock		
Treated		3
Completed		0
Discontinued		3
PD population		3
Safety population		3
Age, weeks	Septic shock	24+ 6, 27+5, 26+6
	Non-septic shock	26+1, 26+1, 24+5
Weight [Mean (SD)], kg	Septic shock	600. 660, 550
	Non-septic shock	890, 880,550
Male/Female	Septic shock	1/2
	Non-septic shock	2/1
Race (Caucasian/Black/Hispanic/ Asian/Other)	Septic shock	Not indicated
	Non-septic shock	Not indicated

The characteristics of the patients and the clinical details are listed in the below table:

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PD

The results of the AVP treatment in the 3 infants with septic shock and 3 infants with non-septic shock are shown in the below 2 figures:

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The increase from baseline in MAP and HR in the infants with septic and non-septic shock were read off from Figures 1 and 2 by the Reviewer, and the mean values are listed in the 2 below tables:

Increase in MAP Relative to Baseline after AVP Infusion in Infants with Septic Shock

Time post infusion start, h	ΔMAP mm Hg	ΔHR bpm
2	8.0	3
4	7.0	0
8	2.4	3
12	5.9	-5
24	0	-15

Increase in MAP Relative to Baseline after AVP Infusion in Infants with Non-Septic Shock

Time post infusion start, h	ΔMAP, mm Hg	ΔHR bpm
2	13.9	3
4	10.9	6
8	6.7	15

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Both groups of infants displayed an increase in MAP relative to baseline when AVP was infused in doses of 0.000167-0.0060 U/kg/min. The pressor effect of AVP continued for 12 h in the infants with septic shock and for 8 in the infants with non-septic shock. The HR did not change in the first 8 h, but fell relative to baseline 12 and 24 h after initiation of the AVP infusion in the infants with septic shock. In the infants with non-septic shock the HR tended to increase during the 8 h of infusion. Urine output increased in both groups during the AVP infusions. The serum lactate levels tended to fall in the septic infants whereas they tended to increase in the infants with non-septic shock.
Safety
▪ Was there any death or serious adverse events? ☑Yes ☐ No ☐ NA ▪ 1 infant with septic shock and 2 infants with non-septic shock died
Conclusion
• After infusions of AVP ranging between 0.000167-0.0060 U/kg/min to ELBW infants with septic and non-septic shock MAP relative to baseline increased for most of the observation period. HR tended to decrease in the infants with septic shock, whereas infants with non-septic shock showed a trend for an increase. • The urine output tended to increase in both groups. The serum lactate levels decreased in the infants with septic shock, but increased in the infants with non-septic shock
Comments
• None

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/s/

PETER HINDERLING
05/24/2013

RAJANIKANTH MADABUSHI
05/28/2013

CLINICAL PHARMACOLOGY REVIEW

NDA Number:	**204485**
Submission Type; Code:	**S, 505 (b)(2)**
Applicant Name:	**JHP Pharmaceuticals**
Submission Date:	**9-25-12**
Brand Name:	**Pitressin®**
Generic Name	**Synthetic vasopressin=8-L-arginine vasopressin**
Dosage Form:	**Intravenous injection**
Dosage Strengths:	**20 Pressor Units/mL in water**
Proposed Indication:	**Vasodilatory shock (including post-cardiotomy shock and septic shock)**
OCP Division:	**DCRP, HFD 110**
Primary Reviewer:	**Peter Hinderling, MD**
Team Leader:	**Rajnikanth Madabushi, PhD**

Reference ID: 3313873

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1 EXECUTIVE SUMMARY

JHS Pharmaceuticals with NDA 204485 seeks approval of Vasopressin Injection, USP (20 U/mL, 1 mL vial). Vasopressin is the synthetic form of 8-L arginine-vasopressin (AVP) which is naturally formed in the posterior pituitary. The sponsor seeks approval via the 505(b) 2 pathway relying on published literature in adults to support clinical pharmacology, clinical safety and efficacy and part of pharmacology and toxicology of the proposed drug product. The sponsor proposed indications for vasopressin include treatment of post-cardiotomy- and septic shock in adults. The sponsor originally sought also an indication for AVP in children with post-cardiotomy shock. However, subsequently the sponsor decided not to recommend administration of AVP to children with post-cardiotomy shock.

There is no listing of a Reference Listed Drug (RLD) in the Electronic Orange Book for Vasopressin Injection, USP. Pitressin® (Parke-Davis) for intravenous injection containing AVP has not been approved. A literature based 505 (b) 2 submission without a RLD is supported by the Guidance for FDA staff and Industry" Marketed Unapproved Drugs-Compliance Policy Guide" Sec. 440,100.

The clinical pharmacology and clinical parts of the submission consist of published literature documenting the hemodynamic effects of AVP in adult healthy subjects and adult patients with the target disease, i.e. post-cardiotomy shock or septic shock. The reviewed studies report on the pharmacology, pharmacokinetics, tolerability, and exposure-response relationship of AVP and the impact of extrinsic and intrinsic factors in adults. In addition, the clinical part of the submission contains publications reporting on the effect of AVP on arterial blood pressure in children with post-cardiotomy or septic shock. However, no information is submitted on the pharmacokinetics of AVP in the pediatric population.

<u>Database</u>

The clinical pharmacology part of the sponsor proposed label is referenced to 10 publications reporting on findings of AVP in adults. The literature search performed by the Reviewer provided 28 additional publications with supplemental clinical pharmacology information. Thirty-four (34) papers, including 7 of the 10 provided by the sponsor, were reviewed. The remaining 3 of the sponsor's publications were not reviewed because they were either superseded by more pertinent publications or not considered relevant. The sponsor submitted 36 publications of clinical studies on AVP reporting experimental findings on efficacy and/or safety of AVP in adults and children. Twenty-five (25) clinical studies were reviewed, that included information on the hemodynamics of AVP.

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1.1 Summary of Important Clinical Pharmacology Findings

The key clinical pharmacology findings on exogenous and endogenous AVP are summarized below:

Adult Populations

- The pharmacokinetics of AVP is infusion rate dependent and characterized by an increase of the clearance with increasing dose. At therapeutic dose levels the pharmacokinetics of AVP in patients with vasodilatory shock approaches dose proportionality
- The apparent t1/2 of AVP is ≤ 10 min
- AVP is eliminated mainly by metabolism involving serine protease, peptidases and oxido-reductases. Only about 7% of the dose of AVP is excreted unchanged in urine.
- The clearance of endogenous AVP is increased 4 times in the second and third trimester of pregnancy without a change in the plasma levels of the hormone indicating that the release rate in the pituitary pool is increased in proportion to the increased disposition. The increase in the clearance of endogenous AVP is due to a spill-over into blood of vasopressinase, an amino peptidase produced in the trophoblast. Similar to endogenous AVP also the clearance of exogenous AVP is significantly increased during the second and third trimester of pregnancy.
- In healthy subjects the onset of the pressor and bradycardia effects of AVP occurs within 5 min of initiation of the infusion, and a maximum effect is attained within 10 min. Thereafter, the effects of AVP fade rapidly and are undetectable prior to infusion stop indicating tachyphylaxis.
- In patients with idiopathic orthostatic hypotension AVP increases mean arterial blood pressure (MAP) significantly more than in healthy subjects and the effect is sustained during the duration of the infusion indicating absence of tachyphylaxis. However, no effect on heart rate (HR) is observed suggesting loss of the baroreceptor mediated reflex in the patients with Shy-Drager syndrome.
- In the target population with vasodilatory shock AVP consistently increases MAP and systemic vascular resistance (PVR), decreases the dose requirements of co-infused norepinephrine (NE) and tends to reduce HR and cardiac index (CI). The opposite effects on MAP (increase) and HR (decrease) suggest that AVP re-establishes the baroreceptor mediated reflex in vasodilatory shock patients. As in healthy subjects and patients with Shy-Drager syndrome the onset of AVP's effect on MAP is within minutes and peak effects occur 15 min after infusion initiation. The offset of the effect on MAP occurs about 30 min after infusion stop. There is no evidence for tachyphylaxis in the patients with vasodilatory shock.

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- A trend for a dose-response relationship exists in patients with vasodilatory shock for AVP's effect on PVR, MAP and NE dose requirements.
- Drug-interactions of AVP with co-administered other drugs are primarily pharmacodynamically based. Exposure based dose adjustments of AVP are not necessary because by titrating the dose to the target MAP response (>65-70 mm Hg) an adjustment of the dose occurs automatically.

Pediatric Population

- As in adults, AVP exhibits a pressor effect in the pediatric population with post-cardiotomy shock or septic shock when body weight normalized adult infusion rates are used.

1.1 Phase 4 Requirements

- None

1.2 Recommendations

- The Office of Clinical Pharmacology (OCP/DCP1) reviewed the submitted literature supporting the clinical pharmacology part of NDA 204485 and recommends, based on AVP's consistent pressor effect on mean arterial blood pressure, approval for the indications catecholamine refractory post-cardiotomy and septic shock in adults

The Office has the following Recommendations/Comments for the label:

<u>Adult Population</u>

- Post-cardiotomy shock: A starting dose of 0.010 U/min should be used which may be up-titrated to a maximum dose of 0.10 U/min to maintain MAP > 65-70 mm Hg. If up-titration is required the dose should be increased stepwise to 0.040, 0.070 and up to 0.10 U/min. An interval of 15 min is to be maintained before the next higher dose is administered.

  Once hemodynamic stability is established the catecholamine dose may be reduced stepwise. After complete weaning from catecholamines the dose of AVP may be decreased stepwise dependent on the individual patient's response.

  Septic shock: A starting dose of 0.010 U/min should be used which may be up-titrated to a maximum dose of 0.070 U/min to maintain MAP > 65-70 mm Hg. If up-titration is required the dose should be increased stepwise to 0.030, 0.050, and up to 0.070 U/min. An interval of 15 min is to be maintained before the next higher dose is administered.

  Once hemodynamic stability is established the catecholamine dose may be reduced stepwise. After complete weaning from catecholamines the dose of AVP may be decreased stepwise dependent on the individual patient's response.

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Pregnancy

- Post-cardiotomy shock and septic shock: Women pregnant up to 11 weeks: Use the usual, respective starting, incremental and maximum doses of AVP if required. Women pregnant 12-21 weeks: Increase respective starting, incremental and maximum doses 2 fold. Women pregnant ≥ 22 weeks: Increase usual, respective starting, incremental and maximum doses 4 fold.

Briefing

The Briefing was held May 23, 2013

2 QUESTION BASED REVIEW

2.1 General Attributes of the Drug

2.1.1 History of Regulatory Development

Parke-Davis introduced natural vasopressin, an extract of the bovine posterior pituitary, into the market in 1928 and obtained the registered trade name Pitressin®. In 1941, Pitressin® Tannate Oil (NDA 3402) for subcutaneous or intramuscular administration was approved for the management of central diabetes insipidus. In 1984 Parke-Davis submitted NDA 19286 seeking the indication "acute gastrointestinal bleeding" for synthetic Pitressin® administered intravenously. NDA 19286 was withdrawn by Parke-Davis in 1984. The earlier NDA 3402 was also withdrawn by Parke-Davis in 1998 for reasons other than safety or effectiveness (CFR 314.150).

JMP Pharmaceuticals acquired the manufacturing site in Rochester MI from Parke-Davis. Currently JMP Pharmaceuticals' Pitressin® administered intramuscularly or subcutaneously is approved for prevention and treatment of post-operative abdominal distention in abdominal roentogenography to dispel interfering gas shadows, and in central diabetes insipidus.

Intravenously administered AVP Pitressin® (Parke-Davis) has been used off label for cardiopulmonary resuscitation, and treatment of gastrointestinal hemorrhage and vasodilatory shock. Diagnostically AVP has been employed to provoke pituitary release of ACTH and growth hormone.

A synthetic vasopressin analogue, mercaptopropionic acid 8-D-argininine monoacetate, desmopressin acetate, DDAVP®, a specific V_2 agonist, is administered as injection solution, tablet, intra-nasal solution or through a rhinal tube. DDAVP® is marketed in the US for the treatment of central diabetes insipidus and nocturnal enuresis. A lysine-

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vasopressin analog, Terlipressin® [N-(N-(N-Glycylglycyl)glycyl)8-L-lysine-vasopressin] is marketed in Europe for the indications septic shock, hepatorenal syndrome and treatment of bleeding esophageal varices.

Vasopressin, arginine-vasopressin and antidiuretic hormone are used interchangeably in the literature. In this review the term AVP is used only when the vasopressin administered is identified as 8-L-arginine-vasopressin. Otherwise the term vasopressin is used which could represent arginine-vasopressin or lysine-vasopressin. The term antidiuretic hormone is not used in this review.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

AVP is an annular nonapeptide containing the following amino-acids: Hi-Cys-Tyr-Phe-Glu(NH2)-Asp(NH2)-Cys-Pro-Gly-(NH2). The two cysteins form a disulfide bridge which gives vasopressin the annular structure seen below:

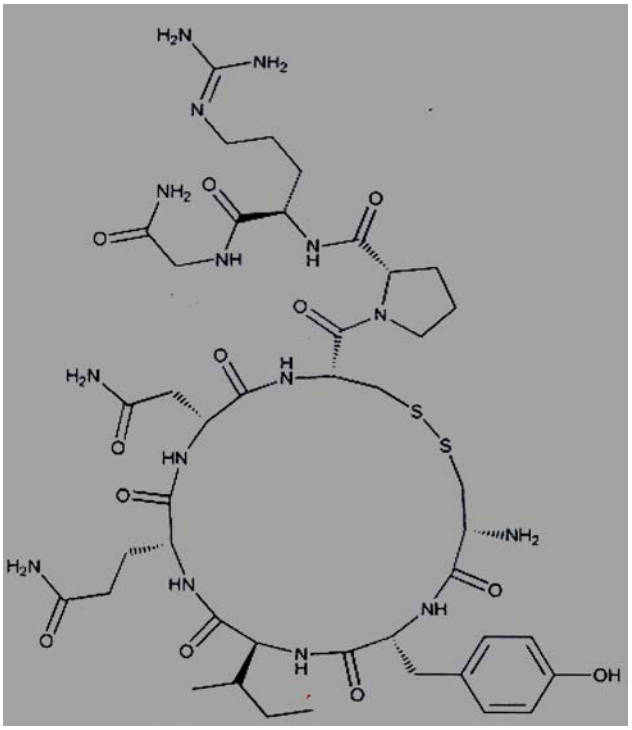

Figure 1. Structure of 8-L-Arginine Vasopressin

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The molecular formula for AVP is $C_{46}H_{65}N_{15}O_{12}S_2$ and the MW is 1084. AVP is soluble in water. The potency of AVP is standardized to contain 20 pressor units/mL in water for injection. One (1) mg AVP is equivalent to 530 U. The solution contains (b) (4) (b) (4), 0.5% chlorobutanol as a preservative and water qs pH (b) (4) adjusted with acetic acid.

2.1.3 What are the proposed mechanisms of action and therapeutic indications?

Therapeutic Indications

Adults

The sponsor seeks the indication "use for hemodynamic support in adult patients with vasodilatory shock, unresponsive to adequate fluid resuscitation and catecholamine administration, including post-cardiotomy shock and septic shock".

Children

Vasopressin is not recommended for use in pediatrics.

Proposed Mechanism of Action

Vasodilatory shock is characterized by hypoperfusion, lactic acidosis and hypotension and often resistant to fluid resuscitation and constant infusion of NE. Vasodilatory shock may be caused by accumulation of central nitric oxide production arising from the inducible nitric oxide synthase and opening of ATP sensitive potassium channels as well as a down-regulation of V_3 receptors.

In the early stages of vasodilatory shock the plasma concentrations of endogenous AVP are increased 20-200 fold. At these elevated levels AVP triggers primarily vasoconstriction and helps in maintaining end-organ perfusion. In later stages of vasodilatory shock the plasma concentrations of endogenous AVP fall, probably as a result of a depletion of the pool in the posterior pituitary. These findings on endogenous AVP were interpreted to indicate that a substitution of endogenous by exogenous AVP could be an effective treatment for vasodilatory shock.

The pharmacology and signal pathways for endogenous AVP at physiological concentrations are mediated by three receptor subtypes V_1 (formerly V_{1a}), V_2 and V_3 (formerly V_{1b}) (1,2). The vascular V_1 receptors are Gq coupled and when activated release phospholipase C and subsequently calcium from intracellular stores. In the kidney vasopressin contracts the mesangial cells in the glomerulus and smooth muscle cells in the vasa recta and efferent arterioles. Binding of AVP to V_1 receptors results in immediate effects such as vasoconstriction. Longer term effects include growth of

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smooth muscles cells. At physiological concentrations of endogenous AVP vasoconstrictor effects are minimal. At pharmacological concentrations AVP is a potent vasoconstrictor in various tissues including skin, skeletal muscles, fat, gastrointestinal tract, coronary vessels and brain. Platelets also express V_1 receptors and stimulation facilitates thrombosis via intracellular calcium release.

The V_2 renal receptors are Gs protein linked. They are located on the basolateral membranes of the distal tubule and collecting duct. Binding of AVP activates adenylcyclase resulting in an increase of cyclic adenosine monophosphate. This triggers formation and insertion of aquaporin channels into the apical membrane. The net result is an increased re-absorption of free water and a decrease in urine output. The homeostasis of the osmotic pressure in plasma is maintained by signals from osmotic receptors titrating the AVP levels by up- or down regulating the rate of secretion from the pool in the posterior pituitary.

The V_3 pituitary receptors when activated use the same signaling pathway as the V_1 receptors. AVP binding to V_3 receptors results in the secretion of ACTH. Additionally, V_3 receptors and AVP act in the central nervous system as modulators and neurotransmitters, respectively, controlling memory, blood pressure and body temperature.

2.1.4 What are the proposed dosages and routes of administration?

Sponsor Proposed Dosages

Adults

Post-cardiotomy shock: A starting infusion rate of 0.03 U/min of vasopressin should be used. Catecholamine doses may be reduced incrementally in a stepwise fashion to maintain hemodynamic stability (target MAP=60-70 mmHg). Once catecholamines are no longer required the infusion rate may be tapered by 0.005 U/min every hour, and discontinued when the MAP is stable at 60-70 mmHg for at least 8 h.

Septic shock: A starting infusion rate of 0.01U/min of vasopressin should be used and increased to 0.03 U/min to maintain hemodynamic stability (target MAP=60-70 mm Hg); A maximum infusion rate of 0.067 U/min may be used. Once catecholamines are no longer required the infusion rate may be tapered by 0.005 U/min every hour, and discontinued when MAP is stable at 60-70 mmHg for at least 8 h.

Proposed Route of Administration

Intravenous Infusion

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2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?

Clinical Pharmacology Studies

Adults

a) open-label, crossover b) open label, randomized, cross-over, c) open-label, placebo controlled, crossover d) single blind, randomized, crossover, placebo controlled

The respective goals of the studies were to investigate the linearity of the PK, intrinsic and extrinsic factors impacting the PK, the mass balance, the pharmacology and tolerability and the exposure-response relationship in healthy subjects and patients

Children

None

Clinical Studies

Adults

Studies in Patients with Post-cardiotomy Shock

a) 1 randomized, double-blind, placebo controlled, b) 5 open-label

These studies investigated the hemodynamics and safety of AVP.

Studies in Patients with Septic Shock

a) 1 randomized, double-blind, placebo controlled b) 2 randomized, double-blind, active controlled (NE) c) 1 randomized, open-label, active controlled (NE) d) 2 open label

These studies investigated the hemodynamics and safety of AVP

Studies in Patients with Status after Post-cardiotomy, Septic Shock or Systemic Inflammatory Response Syndrome

a) 5 open-label studies including 3 studies with different dose levels of AVP (2 studies with parallel groups and 1 study with ascending dose levels in same group), 1 study with NE as control

Children

Studies in Patients with Post-cardiotomy Shock

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a) 2 open-label

Studies in Patients with Septic Shock

a) 1 randomized, double-blind, placebo controlled b) 1 open-label

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Pharmacological doses of exogenous AVP administered intravenously to healthy subjects elicit vasoconstriction in various tissues resulting in increased systemic vascular resistance (SVR) and MAP and a decrease in HR. In addition, AVP contracts the smooth muscles of the gastro-intestinal tract. Paradoxically, AVP administered intra-arterially or intravenously can also elicit regional arterial vasodilation, such as an increase in forearm blood flow (FBF). The response end-points in healthy subjects include systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, HR, SVR, cardiac output (CO), FBF and digital blood flow (DBF). Patients with vasodilatory shock carried catheters allowing the measurement of additional endpoints including central vein pressure (CVP), mean arterial pulmonary pressure (MPAP) and pulmonary artery occlusion pressure (PAOP). The effect of exogenous AVP on splanchnic blood flow was measured by determining the clearance of indocyanine green or by tonometry. The effect of AVP on cutaneous blood flow was assessed by laser Doppler flowmetry. Arterial blood gas analysis provided additional endpoints including systemic O_2 consumption and extraction, and mixed venous O_2 saturation. Additional parameters measured include pH and arterial lactate levels, serum creatinine and urine flow and clinical scores representing measures for organ failure.

2.2.3 Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

<u>Identification of Pharmacological Active Moieties</u>

It is believed that AVP is the main pharmacologically active moiety in the circulation. However, the pharmacological activity of the metabolites of AVP has not been determined.

<u>Moieties Measured in Biological Fluids</u>

Only parent AVP was measured. The acceptability criteria applied for assay methods used to determine PK parameters and exposure of AVP are described in Section 2.6.4

2.2.4 Exposure-Response

Dose range evaluated

AVP has been administered by intravenous injection, and intravenous and intra-arterial infusions in healthy subjects. The intravenous infusions were given over 20-60 min and

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the intra-arterial infusions over 2-20 min. The doses administered by intravenous injection ranged between 0.10 and 9.8 U. The intravenous and intra-arterial infusion rates ranged between 0.00037 and 0.37 U/min and 0.0016 and 0.066 U/min, respectively.

AVP in patients with vasodilatory shock was administered by infusion rates ranging between 0.01-0.15 U/min for several hours to several days.

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy?

Effect of AVP in Healthy Subjects and Patients with Idiopathic Orthostatic Hypotension (Shy-Drager Syndrome)

An intravenous infusion of AVP (0.0032 - 0.17 U/min) increases MAP and reduces HR within 5 min in healthy subjects. These effects are transient and disappear before cessation of the infusion as shown in the below Figure:

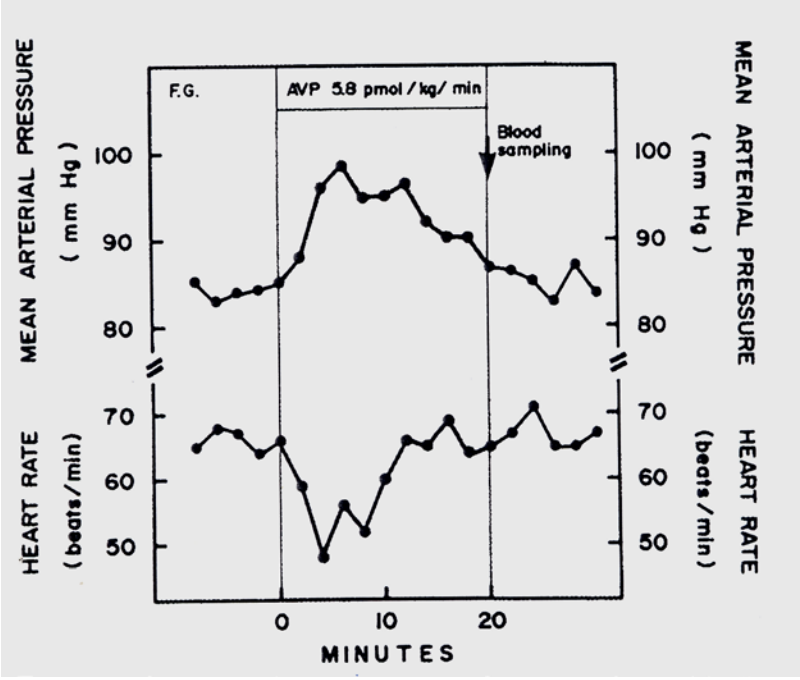

Figure 2: Impact of Infusion of AVP (0.17 U/min) on mean arterial blood pressure and heart rate in a healthy subject (3)

The rise in MAP is the result of an increase in SVR caused by systemic vasoconstriction via V_1 receptors (4, 5). The drop in HR is thought to be a cardiovascular reflex mediated "buffering" of the sudden rise in MAP. Interestingly, AVP in healthy subjects exerts also localized vasodilatory effects as shown by the increase of forearm blood flow (FBF) after intravenous (0.037 -0.37 U/min) and intra-arterial infusions (0.0065-0.032 U/min) (6-8). Receptors and signal pathway mediating the vasodilatory effects of AVP are unknown.

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The regional diversity of the vascular effects of AVP is evidenced by a reduction of digital blood flow (DBF) after intra-arterial infusion (0.037 U/min) (8).

Patients with Shy-Drager syndrome and idiopathic orthostatic hypotension when standing up exhibit a precipitous fall in BP with no change in HR. An infusion of AVP increases MAP within 5 min significantly more than in healthy subjects. In contrast to healthy subjects, patients with Shy-Drager syndrome do not exhibit a reduction in HR suggesting absence of a baroreceptor mediated reflex as shown in the below figure:

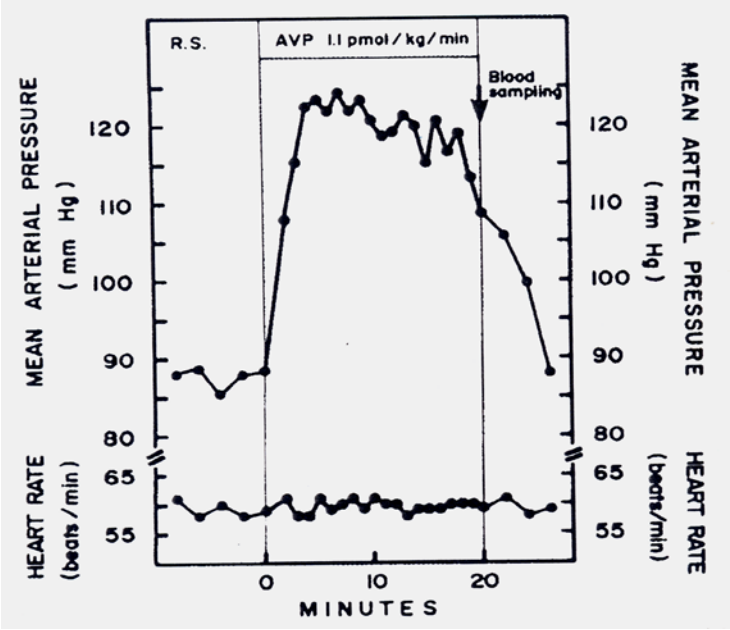

Figure 3. Impact of intravenous infusion of AVP (0.031 U/min) on mean arterial blood pressure and heart rate in a patient with Shy-Drager syndrome and idiopathic orthostatic hypotension (3)

The effect of AVP on MAP in the Shy-Drager patients is sustained. The exposure-effect and dose-effect relationships of AVP in healthy subjects and patients with Shy-Drager Syndrome are quite different as shown in the below figures:

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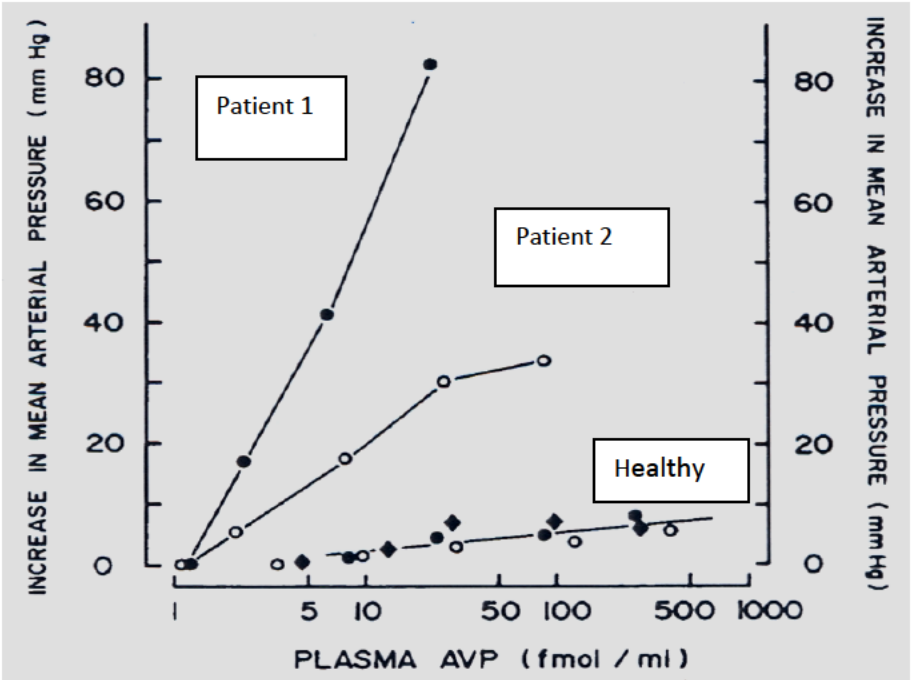

Figure 4. Concentration-exposure relationship of AVP infused into 3 healthy subjects (filled circles and diamonds and open circles at the bottom of the figure) and 2 patients with the Shy-Drager Syndrome (open and filled circles in the middle and upper section of the figure) (3)

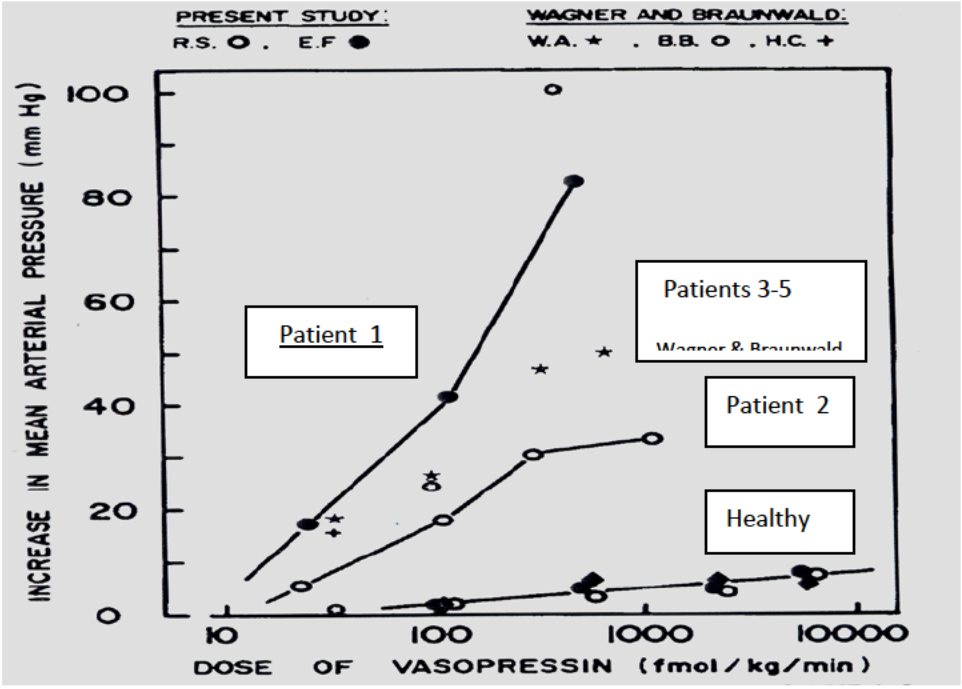

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Figure 5. Dose-exposure relationship of AVP in the above 3 healthy subjects and 5 patients with Shy-Drager Syndrome (3). Data of healthy subjects are in the lower right hand corner of the figure.

The dose- and exposure-effect relationships of AVP in healthy subjects are flat, whereas the corresponding relationships are steep in the patients with Shy-Drager syndrome indicating a greatly increased sensitivity to the vaso-constrictive effects of AVP. Thus, the Shy-Drager syndrome with idiopathic orthostasis is of interest as a possible disease model allowing a better characterization of the effects of AVP than in patients with vasodilatory shock or in healthy subjects.

Effect of AVP in Adult Patients with Vasodilatory Shock

Characteristics of the Individual Clinical Trials Measuring the Hemodynamics of AVP

Hemodynamic results on AVP are available from 17 clinical trials that enrolled patients with post-cardiotomy shock, septic shock or shock due to systemic inflammatory response syndrome (SIRS). Some of the studies enrolled exclusively patients with post-cardiotomy shock or septic shock. Other studies enrolled patients with different shocks including post-cardiotomy, sepsis and shock due to SIRS. Shock was defined as a status characterized by MAP <70 mm Hg despite fluid resuscitation and infusion of catecholamines, primarily norepinephrine (NE). The rates of NE infusion among the studies varied greatly. Only 1 study did not require catecholamine refractoriness as inclusion criterion. A cardiac index (CI) > 2.0 L/min/m^2 was required in most studies. In 4 studies patients on primarily milrinone with CI < 2.0 L/min/m^2 were enrolled.

During administration of AVP open-label NE was co-infused and the rate was adjusted to maintain MAP > 70 mm Hg. In the large majority of the trials NE could be tapered off and stopped entirely, if the infusion rate could be reduced below a critical threshold value for a defined time interval. AVP could be tapered off only once a patient was weaned from NE completely.

All 17 clinical studies contained information on the effect of AVP on MAP. In addition, most studies provided information on the effects of AVP on SVR, HR and CI. A number of studies measured also the changes of the dose requirements of NE in the patients receiving AVP. A number of studies measured the hemodynamic variables only at one time point after initiation of the AVP infusion. Several studies measured the hemodynamic variables at multiple time points up to 48 h after initiation of the AVP infusions. Given the variability induced by tapering off open label NE and in order to quantify the true net effect of AVP, as much as possible the earliest common time point

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after initiation of AVP with a hemodynamic measurement was selected by the Reviewer to compare the pharmacological effects of AVP from different studies. As will be shown later, onset and attainment of the full effect of AVP in patients with vasodilatory shock occurs within 10-15 min of infusion start as in patients with Shy-Drager syndrome and healthy subjects. The results of the effect of AVP and vasopressin on mean MAP, the pharmacological endpoint of primary interest, are reported in tables separately for each study. The pooled results on mean SVR, MAP, HR, CI and NE dose requirements from all studies with patients with vasodilatory shock are reported in figures.

Trials Measuring Hemodynamics of AVP in Patients with Post-cardiotomy Shock

Information on changes from baseline in MAP after infusion of AVP, identified as Pitressin® (Parke-Davis) the reference for the sponsor's AVP, was available from 1 randomized, double-blind, placebo controlled study and 5 open-label studies in patients with post-cardiotomy shock. All studies required a CI > 2.5 L/min/m^2. Only Duenser et al 2002 enrolled patients with a CI < 2.0 L/min/m^2 and on milrinone (13).

The effects of AVP on MAP in the studies conducted in patients with post-cardiotomy shock, are listed in the below table:

Table 1. Trial Characteristics and Effect of AVP on the Baseline Corrected Mean Arterial Blood Pressure (ΔMAP) in all Studies and on the Baseline and Control Corrected Mean Arterial Blood Pressure (ΔΔMAP) in the Randomized, Double-Blind, Controlled Study in Patients with Post-Cardiotomy Shock

Study	**n[a]**	**Rate[a]**	**PD Time**	**ΔMAP[b]**		**ΔΔMAP[c]**
		U/min	**h**	**mm Hg**		**mm Hg**
RDBPC[d]				**AVP**	**Placebo**	**AVP**
Argenziano 1997 (9)	5	0.10	0.25	27	2	25
OL[e]				**AVP**		
Argenziano 1998 (10)	40	0.10	0-2.0[f]	24		na
Argenziano 1999 (11)	20	0.10	1.0	26		na
Morales 2000 (12)	50	0.090	0.25	17		na
Duenser 2002 (13)	41	0.084	1.0	27		na

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Luckner 2006 (14)	18	0.067	1	17	na

[a] number of subjects receiving AVP arm [b] baseline corrected mean arterial blood pressure [c] baseline and placebo corrected mean arterial blood pressure [d] randomized, double-blind, placebo controlled [e] open-label [f] peak effect na=not applicable

The data indicate a consistent pressor effect on MAP in all 6 studies in patients with post-cardiotomy shock when AVP was infused at rates between 0.067 and 0.10 U/min.

The study by Argenziano et al 1998 indicates that the increase in MAP exerted by AVP is inversely proportional to the baseline MAP as shown in the below figure:

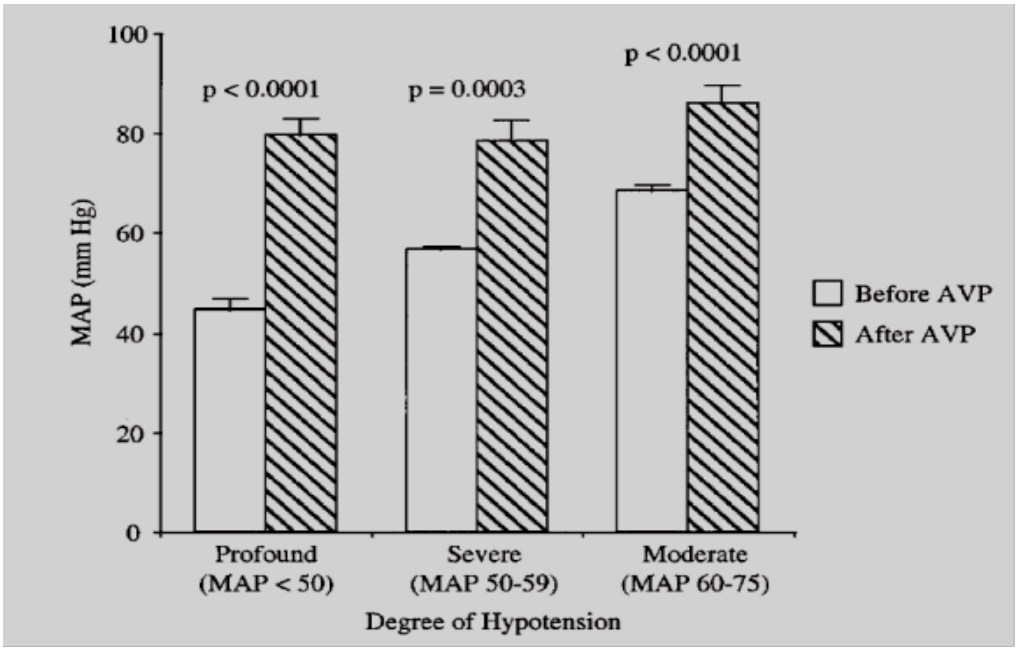

Figure 6: Plot of MAP at baseline and at peak MAP during AVP infusion in 3 groups of patients with different degrees of hypotension

The findings are suggestive for the existence of a dose-response relationship for AVP in patients with post-cardiotomy shock.

Estimates for the inter-subject variability of the pressor effect of AVP are available from 2 studies with patients with post-cardiotomy shock as shown in the below table:

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Table 2. Coefficient of Variation about Mean ΔMAP in Post-cardiotomy Shock

Study	**CV,%**
Argenziano (1997)	58
Argenziano (1998)	62

Trials Measuring the Hemodynamics AVP or Vasopressin in Patients with Septic Shock

Information on changes from the baseline in MAP after infusion of AVP or vasopressin in patients with septic shock was available from 3 randomized, double-blind, controlled studies, 1 randomized, open-label, active control study and 2 open-label studies. There were significant differences in the design of the studies (see Table 3). The study by Lam et al did not apply a minimal CI value as additional inclusion criterion (19). The study by Malay et al used AVP Pitressin® (Parke-Davis) and iso-saline as control (15). The studies by Patel et al and Russell et al used NE as control, but the respective publications did not state the type of vasopressin administered (16,17). Similarly, the open-label studies by Landry et al. and Lam et al. did not state the vasopressin used in their trials (18,19). The subjects in the study by Lam et al did not receive catecholamines prior to or during the administration of AVP (19). The open-label study by Lauzier et al used AVP (Ferring, Toronto) and NE as control (20). The study by Russell et al used dextrose 5% as diluent resulting in partial degradation of vasopressin.

The effects of AVP and vasopressin on MAP in patients with septic shock are shown in the below table:

Table 3. Trial Characteristics and Effect of AVP on the Baseline Corrected MAP (ΔMAP) in all Studies and on the Corrected Mean Arterial Blood Pressure (ΔΔMAP) in the Randomized Double-Blind, Controlled and Randomized, Open-label Controlled Studies in Patients with Septic Shock

Study	**n[a]**	**Control**	**Rate[a,b]**	**PD Time**	**ΔMAP[c]**		**ΔΔMAP[d]**
			U/min	**h**	**mm Hg**		**mm Hg**
RDBPC[e]					**AVP**	**Placebo**	**AVP**
Malay 1999 (15)	5	Isosaline	0.040	1	15	2	13
RDBAC[f]					**AVP**	**NE**	**AVP**
Patel 2002 (16)	13	NE	0.060	4	0	-1[g]	1

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Russell 2008 (17)	397	NE	0.030	4	1[h]	2[h,i]	3
ROLAC[k]							
Lauzier 2006 (18)	13	NE	0.15	1	2	4[l]	-2
OL[m]					**AVP**		
Landry 1997 (19)	10	none	0.040	0-1	29		na
Lam 2008 (20)	66	none	0.067	1	14		na

[a] number of patients receiving AVP or vasopressin [b] infusion rate of AVP or vasopressin [c] baseline corrected mean arterial blood pressure [d] baseline and placebo or active control corrected mean arterial blood pressure [e] randomized, double-blind placebo controlled study [f] randomized, double-blind, active controlled study [g] 20 µg/min [h] read off from Figure 1 in Supplement of article [i] 5-15 µg/min [k] randomized, open-label active controlled study [l] 0.7- 196 µg/min [m] open-label study na= not applicable

The results indicate significant effects on MAP in the studies by Malay et al, Landry et al and Lam et al, when AVP or vasopressin was infused at rates of between 0.040 and 0.067 U/min (15. 19, 20). A small effect on MAP relative to baseline was also observed in the study by Lauzier et al using a high rate of 0.15 U/min AVP. However, there was no difference between treatment arms. In the study by Patel et al (16) no effect was observed, even though the dose of vasopressin was intermediate. There was a significant dose sparing of NE in the presence of vasopressin. The study by Russell et al (17) showed no effect on MAP with vasopressin or NE in the early phase after initiation of the study treatments. Of note the baseline MAP exceeded 70 mm Hg in the study by Russell et al raising doubts whether the patients were in shock.

<u>Trials Measuring the Hemodynamic of AVP in Patients with Vasodilatory Shock due to Status after Post-cardiotomy, Sepsis or Systemic Inflammatory Response Syndrome</u>

Information on the effect of AVP on MAP were available from 5 open label studies (Duenser et al 2003 (21), Luckner et al 2005 and 2007 (22,23), Nygren et al (24) and Torgersen et al (25). There were significant differences between the studies. The study by Duenser et al 2003 used an active controlled (NE) design. The studies by Nygren et al, Torgersen et al and Luckner et al. 2007 tested the impact of more than one infusion rate on MAP and other hemodynamic variables. Luckner et al. 2005, Duenser et al 2003 and Nygren et al. used Pitressin® (Parke-Davis), whereas the study by Torgersen et al administered AVP (Ferring). The study by Luckner et al 2007 used. The studies by Torgersen et al. and Nygren et al used CI > 2.5 L/min as a selection criterion whereas the studies by Duenser et al. 2003 and Luckner et al 2005 and 2007 included patients with CI < 2.0 L/min/m^2 and on positive inotropic drugs (21-25).

The below table shows the type of shock the patients presented with in the 5 studies:

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Table 4. Representation of Shocks in Studies Enrolling Patients with Shocks of Different Etiologies

Study	**% Patients Presenting with Different Types of Shock**		
	Post-cardiotomy	**Sepsis**	**SIRS[a]**
Duenser 2003 (21)	42	29	29
Luckner 2005 (22)	43	33	25
Luckner 2007 (23)	33	46	21
Nygren (24)	50	50	0
Torgersen (25)	12	52	36

[a] Systemic inflammatory response syndrome

Patients with post-cardiotomy and septic shocks were more often enrolled than patients with SIRS in these studies.

The effects of AVP and vasopressin on MAP in the patients with shock of mixed etiology are shown in the below table:

Table 5. Trial Characteristics and Effect of AVP and Vasopressin on Baseline Corrected Mean Arterial Blood Pressure (ΔMAP) in the Uncontrolled, Open-label Studies and the Baseline and Control Corrected Mean Arterial Blood Pressure (ΔΔMAP) in the Cotrolled Open Label Study in Patients with Shock due to Status after Post-cardiotomy, Sepsis or Systemic Inflammatory Response Syndrome

Study	**n[a]**	**Rate[a]**	**PD Time**	**ΔMAP[b]**		**ΔΔMAP[c]**
		U/min	**h**	**mm Hg**		**mm Hg**
ROLAC[d]				**AVP**	**NE**	**AVP**
Duenser 2003 (21)	24	0.067	1	19	4[e]	15
OL[f]				**AVP**		
Luckner 2005 (22)	316	0.067	1	23		na
Luckner 2007 (23)	39	0.033	1	19		na
		0.067	1	28		na
Nygren (24)	8	0.020	0.5	3		na

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		0.040	0.5	2	na
		0.080	0.5	2	na
Torgersen (25)	25	0.033	1	6	na
		0.067	1	13	na

[a] number of patients receiving AVP or vasopressin [b] baseline corrected mean arterial blood pressure [c] baseline and active control corrected mean arterial blood pressure [d] ROLAC randomized, open-label, active controlled study [e] < 2.26µg/kg/min [f] open-label study na=not applicable

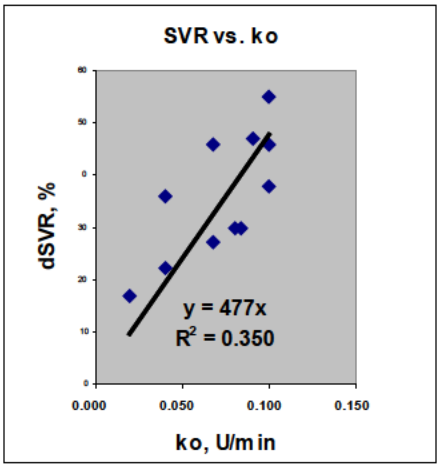
Four (4) of the 5 studies show a consistent pressor effect in the patients receiving AVP or vasopressin at rates ranging between 0.33-0.067 U/min. Only a small pressor effect with AVP is found in the study by Nygren et al. The studies by Luckner et al. 2007 and Torgersen et al suggest that the effect of AVP is dose dependent.

Dose-Response Relationship of AVP Pitressin® (Parke-Davis) for Mean Arterial Blood Pressure, Systemic Vascular Resistance, Heart Rate, Cardiac Index and Norepinephrine Dose Requirements in Patients with Vasodilatory Shock

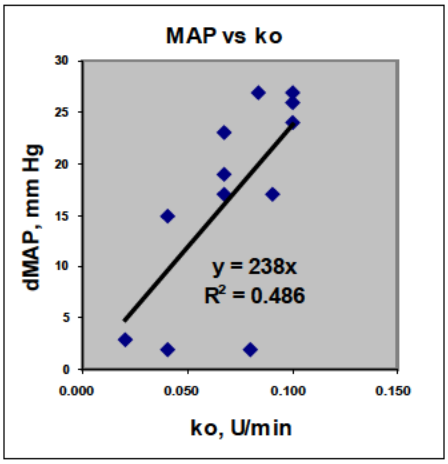
The reference for the sponsor's AVP is AVP Pitressin® (Parke-Davis). As discussed above, a majority but not all 17 clinical trials in adults administered AVP Pitressin® (Parke-Davis). The below figures show the naïve pooled data in plots of the effects of AVP Pitressin® (Parke-Davis) on SVR, MAP, HR and CI in the patients with vasodilatory shock (post-cardiotomy, sepsis, SIRS). Also, included is a plot of the percent reduction in the dose requirements for NE (DNE) when AVP is co-administered in the patients with shock.

Reference ID: 3313873

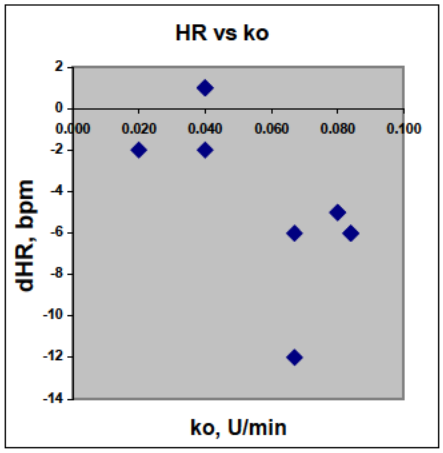
a



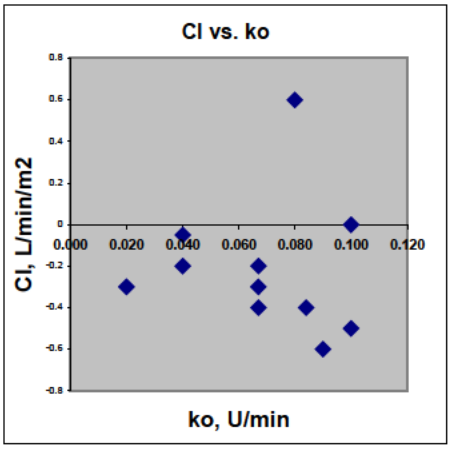
b



c



d



e

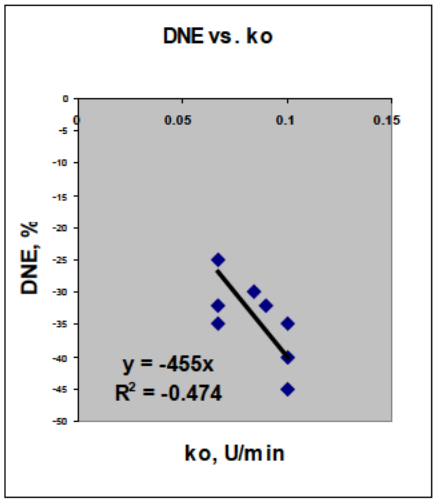


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Figure 6 a,b,c,d,e : Plots of % change from baseline in systemic vascular resistance, baseline corrected mean arterial blood pressure, heart rate and cardiac index and % change from baseline in norepinephrine dose requirements (DNE), respectively, vs. the infusion rate, ko, in patients with vasodilatory shock or SIRS receiving AVP Pitressin® (Parke-Davis). The effects of AVP were measured within the first 2 h after initiation of the AVP infusions. Statistically significant correlations baseline corrected SVR, MAP or DNE requirements exist (Spearman Rank coefficient, $p < 0.05$). The relationship between the effect of AVP on HR or CI and infusion rate of AVP show more variability.

The effects of AVP on the hemodynamics parameters MAP, SVR, HR and CI presented above were measured in the first 2 h after initiation of the AVP infusions. The studies that measured the hemodynamic parameters at later times up to 48 h after initiation of the infusions show sustenance of the pressor effect of AVP.

The below tables summarize the hemodynamic effects of AVP in the target population with vasodilatory shock and compare the pharmacodynamics of AVP in the patients with vasodilatory shock with those in patients with Shy-Drager syndrome and healthy subjects:

Table 6. Changes in Baseline Corrected Hemodynamic Parameters in the Target Population with Vasodilatory Shock by AVP Pitressin® (Parke-Davis)

SVR	MAP	HR	CI	NE Dose Requirements
↑	↑	(↓)	(↓)	↓

Table 7. Pharmacodynamics of the Pressor Effect of AVP on Mean Arterial Blood Pressure in Healthy Subjects, Patients with Shy-Drager Syndrome and Patients with Post-cardiotomy Shock, Septic Shock or Shock of Mixed Etiology

Subjects	**Effect on MAP**		
	Onset	**Offset**	**Tachyphylaxis**
Healthy	Within 5 min	During infusion	Yes
Shy-Drager	Within 5min	≤ 20 min after infusion stop	No
Vasodil. Shock	≤ 15 min	≤ 30 min after infusion stop	No

Reference ID: 3313873

The fast onset and offset of the effect of AVP provides maneuverability in titrating and allows rapid achievement of drug levels eliciting the target pressor effect.

Effect of AVP when Administered Prophylactically in Patients Undergoing Cardiopulmonary Bypass

Three (3) randomized, double-blind, controlled studies investigated the impact of AVP or vasopressin infused at a rate of 0.03 U/min into patients undergoing cardiopulmonary bypass (CPB) who were on ACE inhibitors (26-28). The study by Morales et al 2003 (26) suggests that a vasopressin infusion initiated 20 min prior to the start of CPB and lasting up to 72 hours, if required, reduces the incidence of hypotensive episodes relative to isosaline. The study by Papadopoulos et al (27) shows a significant reduction of the incidence of vasodilatory shock when AVP is infused instead of isosaline. The study by Hasija et al. (28) shows that an infusion of vaasopressin, initiated at the time of re-warming and continued until attainment of stable hemodynamics without vaso-pressor agents, prevents post-CPB hypotension. The results of the 3 studies demonstrate pressor effects of AVP or vasopressin in subjects not in shock but exposed to surgical procedures, anesthetic and antihypertensive drugs, known to possibly induce hypotension. The results of these studies support the findings that AVP or vasopressin exerts pressor effects in patients with vasodilatory shock.

Exposure-Response of V_3 Receptor Mediated Pharmacological Effects of Arginine-Vasopressin on the Pituitary-Hypothalamic Axis

The below tabulated results show the effects of AVP injections and infusions on the pituitary-hypothalamic axis in healthy subjects and patients with advanced vasodilatory shock (29-31):

Healthy Adults

Table 8. Fold Increase in Average Exposure to ACTH and Prolactin after Injection of AVP relative to Saline

AVP		**ACTH**	**Prolactin**
Mode of Administration	**Dose**	**AUC 0-1h**	**AUC0-1h**
	U		

Reference ID: 3313873

iv Bolus	9.8	2.3	1.4

Table 9. Fold Increase in Exposure to ACTH and Cortisol after Administration of AVP relative to Saline

AVP		**ACTH**	**Cortisol**
Mode of Administration	**Dose**	**Cmax**	**Cmax**
	ng/min[a]		
iv Infusion	100	2.1	1.8
	300	4.2	3.0

[a] Factor for converting ng to U not known for AVP (Ferring) administered

AVP administered by intravenous bolus or infusion increases the exposure to ACTH and prolactin. The intravenous infusion mode appears to be more effective than the bolus mode of administration for AVP. The respective peak effects of AVP on ACTH and cortisol occur at 20 min and 60 min after infusion start of AVP.

Patients with Advanced Vasodilatory Shock

Table 10. Fold Increase in Plasma Concentrations after Initiation of an Infusion Containing AVP or Isosaline in Patients with Advanced Vasodilatory Shock due to Status after Post-cardiotomy, Sepsis or Systemic Inflammatory Syndrome

AVP		**Prolactin**
Mode of Administration	**Dose**	**Cmax**
	U/min	
iv Infusion	0.067	2.0

Reference ID: 3313873

A comparison of the results in healthy subjects and patients with vasodiatory shock suggest that an intravenous infusion is more effective than a bolus in increasing prolactin levels. Because of the effects on ACTH and prolactin AVP is considered a “stress hormone”.

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

Healthy subjects

Transient facial pallor, and abdominal discomfort lasting a few minutes have been reported after intravenous injection of AVP (9.8 U) in healthy subjects (26). Nausea, facial pallor, abdominal discomfort, flatulence and urge to defecate were observed after intravenous infusion of AVP (0.064 and 0.17 U/min) (3,4,30). Facial pallor reflects cutaneous vasoconstriction by AVP. The abdominal symptoms indicate smooth muscle contraction in the gastrointestinal tract.

Patients with vasodilatory shock

Safety concerns with AVP include the potential for gastrointestinal and digital ischemia. An open-label study in 12 patients with septic shock receiving serial infusions of NE (0.18-1.1 μg/kg/min), vasopressin (0.060-1.8 U/min) and NE shows that replacement of NE by vasopressin reduces the gastric regional PCO2 gap (32) suggesting increased vasoconstriction of the gastric mucosa by vasopressin relative to NE. Another open-label study investigating cutaneous vascular reactivity and flow motion in 18 patients with vasodilatory shock having undergone cardiotomy or other major surgery and receiving either AVP + open-label NE (> 0.5 μg/min/kg) or open-label NE alone shows no significant difference in cutaneous reactive hyperemia and oscillatory pattern of vascular tone between treatments (14).

2.2.4.3 Does this drug prolong the QT/QTc Interval?

A thorough QT/QTc study with exogenous AVP was not performed. QTc/QT interval measurements after AVP or vasopressin were not reported in the published studies either. However, arrhythmias (ventricular fibrillation, Torsade de pointes, bradycardia) have been reported after infusions of AVP and vasopressin (0.2-1.3 U/min) or 8-L-ornithin vasopressin (0.033-0.067) in patients with alcoholic cirrhosis or hepatitis (33-36).

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known E-R relationship?

Yes. For post-cadiotomy shock the sponsor proposes a starting dose of 0.030 U/min that, if required, can be stepwise up-titrated to 0.1 U/min. For septic shock the sponsor proposes a starting dose of 0.010 U/min that, if required, can be up-titrated stepwise to

Reference ID: 3313873

0.067 U/min. The sponsor proposed respective ranges for the infusion rates of AVP are 0.03 to 0.10 U/min in post-cardiotomy shock and 0.01 to 0.067 U/min in septic shock. These dose ranges correspond to those used in the respective clinical trials.

The aggregate information from the studies in patients with vasodilatory shock suggests an apparent linear dose-response relationship for the effect of AVP Pitressin® (Parke-Davis) on MAP spanning the range of starting and maximum dose proposed by the sponsor. The relationship between dose and occurrence of gastric and digital ischemia potentially caused by AVP or vasopressin in patients with vasodilatory shock is less well defined. High acute doses of AVP administered by intravenous injection have been tolerated by healthy subjects, but extrapolating these results to patients with vasodilatory shock receiving infusions of AVP for various durations may not be appropriate. Published case reports indicate occurrence of cardiac arrhythmias at rates of 0.2-1.3 U/min AVP or vasopressin in patients with liver disease.

The sponsor does not indicate what dose increments of AVP and time intervals between consecutive doses given during the up-titration process should be. The dose increments should be constant because the dose-response of the pressor effect of AVP appears to be linear. The administration of consecutive doses during up-titration should be separated by 15 min because the full effect of AVP evolves over a period of 15 min.

The sponsor proposed procedures for a sequential withdrawal of catecholamines and AVP once hemodynamic stability is attained in patients with vasodilatory shock are reasonable: The dose of catecholamines may be reduced stepwise while maintaining hemodynamic stability. If catecholamines are no longer required the dose of AVP may be tapered. However, the proposed fixed dose decrement of 0.0050 U/min every hour and the requirement for MAP to be stable for 8 h before discontinuing AVP are not supported by the procedures used in the published trials. Therefore, the withdrawal of AVP should use dose decrements and intervals appropriate to the patient's individual response.

2.2.5 What are the PK characteristics of the drug?

Healthy Adult Subjects

Pertinent and acceptable data were available from 4 clinical studies that used AVP Pitressin® (Parke-Davis) (37-40). Of note, the data available were steady-state concentrations and amounts excreted of unchanged AVP after 60-75 min infusions. The clearance (CL) of AVP in healthy subjects and patients with the target disease was calculated from the ratio of the infusion rate (ko) to the steady-state concentrations (Css) of endogenous + exogenous AVP. The concentrations of endogenous AVP were not subtracted from the total concentrations of AVP. At the tested infusion rates the Css of exogenous AVP exceeded those of endogenous AVP greatly.

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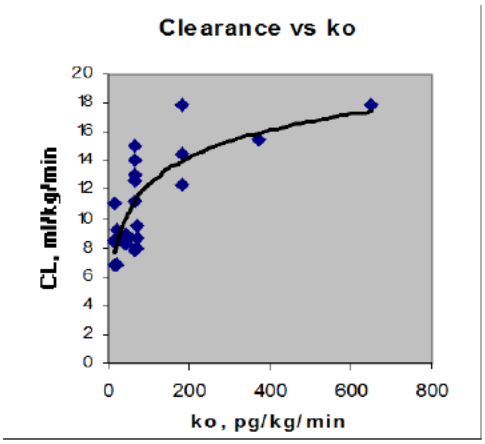
During constant infusions of 60-75 min at rates varying 35 fold, AVP attains an apparent steady-state within ≤ 30 min. The steady-state CL increases with increasing infusion rate suggesting nonlinear PK of AVP as shown in the below figures:



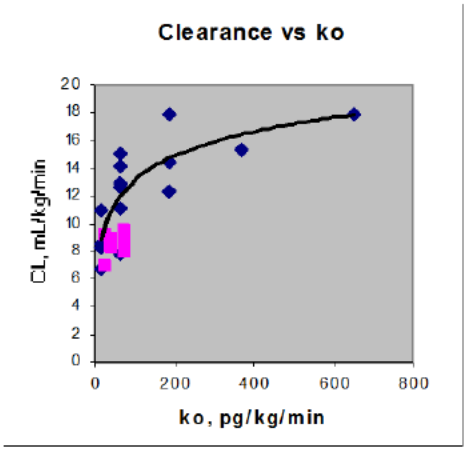
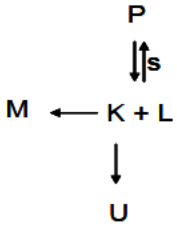


Figure 7a. Data of (37,38), solid trend line

Figure 7b. Blue diamonds: data in males and females (37,38), purple rectangles are data females from (39,40). The solid line is a trend line

The dose dependency of the PK of AVP in healthy subjects at sub-therapeutic levels is also supported by (41). With infusion rates ranging 35 fold, renal clearance (CL_R) increases proportional to CL as evidenced by the constant mean (SD) ratio of CL_R/CL= 0.070 (0.017) (37,38). These results imply that renal excretion of unchanged AVP and metabolism of AVP do not compete, but rather act in concert with each other as shown in the below model:



where P, K, L, M and U stand for plasma, kidney, liver, metabolized drug and drug excreted unchanged in urine, respectively, and s indicates that the backward rate constant from liver and kidney into plasma decreases with increasing dose. Thus, the observed similar dose dependency of CL and CL_R appears to point to an increase in distribution of AVP with dose and not to an accelerated elimination rate constant at higher doses. The available data do not allow a determination of the volume o distribution (V_D). However, a

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rough estimate for the apparent half-life (t1/2) of AVP at therapeutic dose levels obtained from the time required to attain steady-state is ≤ 10 min.

Patients with Status after Cardiotomy

Data are available from 3 studies (24, 26, 29). The below figure shows the mean CL values for AVP in patients with vasodilatory shock and in post-cardiotomy patients without shock together with the data from healthy subjects:

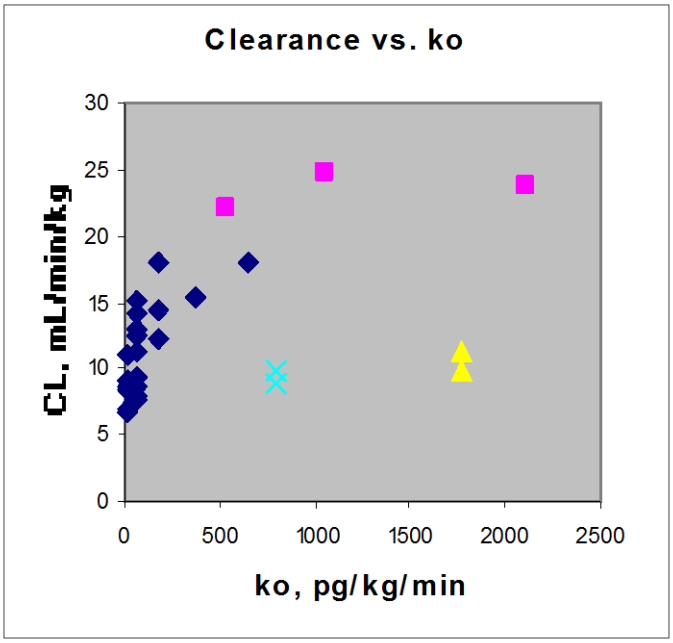

Figure 8: Blue diamonds: Healthy volunteers (37-39), purple squares: Patients with vasodilatory shock due to status post-cardiotomy or systemic inflammatory syndrome) (24), yellow triangles: Patients with vasodilatory shock (post-cardiotomy, systemic inflammatory response syndrome, sepsis) (29), blue crosses: Post-cardiotomy patients without shock (26)

The results indicate that at therapeutic dose levels the PK of AVP approach dose independency. The inter-subject variability of the PK of AVP in the patients appears to be greater than in healthy subjects. The inter-study variation in CL may be explained in part by possibly different conditions of the patients enrolled in the different studies.

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Alternatively, differences in the specificity of the RIA methods used could contribute to the variability of CL observed in the patients.

The respective coefficient of variation about mean CL and Css of AVP are shown for patients with vasodilatory shock and healthy subjects in the below table:

Table 11. Coefficient of Variation about Mean Css or CL of AVP in Healthy Subjects and Patients with Vasodilatory Shock

Author	**Population**	**Range CV, %**	
		CL	**Css**
Moses & Steciak 1986 (37)	Healthy Subjects	8.9-23	
Davison et al. 1989 (39)	Healthy Subjects	27-50	
Nygren et al. 2009 (24)	Post-cardiotomy Shock		32-36
Duenser et al. 2004 (29)	Advanced Vasodil. Shock		34-50

Endogenous AVP

Healthy Subjects

Apart from oscillations due to changes in osmotic pressure, endogenous AVP levels are known to increase when changing from the recumbent to the sitting or standing position, exercising or smoking (42-44). The mean CL_R of endogenous AVP of 21 mL/min estimated in ambulatory, non-smoking subjects is comparable to the CL_R of 27 mL/min for exogenous AVP obtained at one of the lowest infusion rates tested in healthy subjects (37, 42).

Patients with Vasodilatory Shock

The levels of endogenous AVP in vasodilatory shock are increased early and are abnormally low in later stages (18, 45). Stress conditions associated with other serious conditions such as acute respiratory failure or status after cardiotomy increase the levels of endogenous AVP as well (45-47). Significantly increased plasma levels of endogenous AVP have also been reported in patients with end-stage renal disease (ESRD) (48).

2.2.5.1 What are the single and multiple dose PK parameters?

PK parameters of AVP are available following single and multiple constant rate infusions of up to 60-75 min duration in healthy subjects. The CL of AVP increases dose

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dependently from about 7 to 18 mL/kg/min when the infusion rate increases from 0.018 to 0.648 ng/kg/min (about 0.00067- 0.024 U/70 kg/min)

2.2.5.2 How does the PK of the drug and its major metabolites in healthy adults compare to that in patients?

The infusions of AVP in patients with vasodilatory shock last from few hours to days and are longer than the 60-75 min infusions tested in healthy subjects. The rates of AVP administered to the patients with vasodilatory shock ranging between 0.01 and 1.8 U/min are greater than those tested in healthy subjects.

2.2.5.3 What are the characteristics of drug absorption?

AVP is administered by the intravenous route.

2.2.5.4 What are the characteristics of drug distribution?

There are no reliable results on the plasma protein binding and red cell partitioning of AVP in healthy subjects. Because only plasma concentrations at steady-state for AVP were available, no reliable estimates for V_D can be provided.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Quantitative information on the relative contribution of renal vs. metabolic elimination of AVP is available from studies with unlabeled AVP indicating that metabolism is the major route of elimination (93% of the dose), whereas only 7% of the dose is excreted as unchanged drug in urine (37,38). Quantitative information on the contributions of parent drug and metabolites to total radioactivity in the circulation is not available from the mass balance study using ^{125}I-AVP (49).

2.2.5.6 What are the characteristics of drug metabolism?

Metabolism is the main route of elimination for AVP. The metabolic clearance increases with increasing infusion rate. Findings in animals and man show that the enzymes listed in the below table and scheme are involved in the breakdown of AVP:

Table 12. Enzymes Metabolizing AVP, Cleavage Sites and Generated Metabolites

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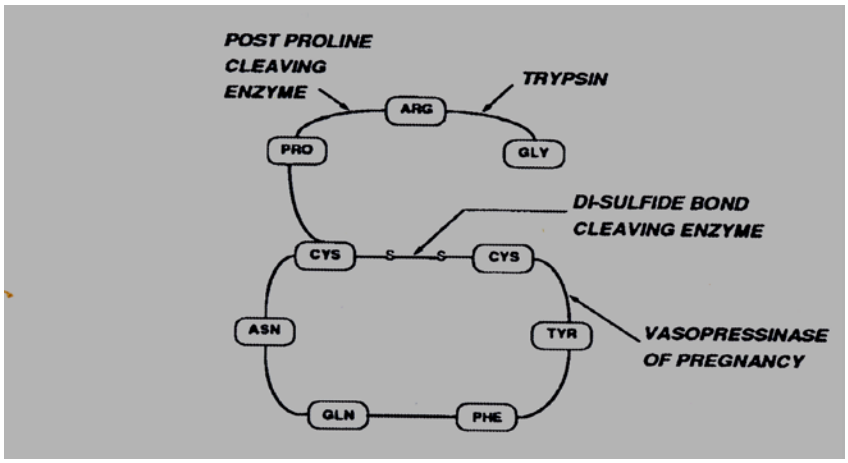
Vasopressin Enzyme	Type	Source(s)	Cleavage Site on Molecule	Metabolites
Post-proline cleaving enzyme	Serine protease	Kidney (several species)[34] Brain extracts[34]	*Tail portion:* Between positions 7 & 8 (PRO-ARG bond)	Arg-Gly-NH_2
Trypsin-like enzyme	Carboxypeptidase	Amniotic fluid[35]	*Tail portion:* Between positions 8 & 9 (ARG-GLY bond)	Gly-NH_2 Desglycinamide AVP
Disulfide bond cleaving enzyme	Thiol:protein disulfide oxidoreductase	Bovine liver[38] Bovine pancreas[37]	*Ring portion:* Disulfide bond	
Vasopressinase	Aminopeptidase	Plasma of pregnancy[34,26] Placenta[26]	*Ring portion:* Between positions 1 & 2 (CYS-TYR bond)	

The specific sites of cleavage for the individual enzymes are depicted in the below scheme:



The main enzymes include serine protease, and carboxypeptidase which cleave in the tail portion of AVP, whereas sulfide oxido-reductase cleaves in the ring portion of AVP. Integrity of the tail- and ring portions of AVP are important for maintaining the pharmacological activity (39,50,51). However, the pharmacological activity of the metabolites has not been tested experimentally.

2.2.5.7 What are the characteristics of drug elimination?

About 7% of the dose is eliminated as unchanged AVP in urine. The CL_R increases from 0.39 to 1.2 ml/min over the range of infusion rates tested. In the absence of reliable information on plasma protein binding, the contribution of glomerular filtration and net tubular secretion or re-absorption to the excretion of AVP cannot be estimated. Data in animals suggest that the kidney together with the liver contributes importantly to the metabolic elimination of AVP (51, 52).

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2.2.5.8 Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?

The dose-concentration relationship of AVP is nonlinear and characterized by an approximately 2.5 fold increase of CL in healthy subjects when the infusion rate is increased by a factor of 35. See also 2.2.5

2.2.5.9 How do the PK parameters change with time following chronic dosing?

When AVP is administered to healthy subjects repetitively by 75 min infusions the PK are not time dependent.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in healthy volunteers and patients?

The median (range) coefficient of variation about the CL of AVP is 43 (20-98) % and 37 (27-49) % (37,38). The intra-subject variability of the CL for AVP is not known.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

A change in body mass between <25 and ≥ 35 kg/m^2 has no impact on the hemodynamic response to vasopressin infused at a rate of 0.04 U/min suggesting a weight based dosage regimen as used with vasopressor catecholamines may not be required for AVP (19).

2.3.2 Based upon what is known about E-R relationships and their variability, what dosage regimen adjustments are recommended for each group?

2.3.2.1 Elderly

No information is available on the exposure-response relationship in elderly vs. young subjects with the target disease. However, this is not a concern, because AVP is up-titrated to the target effect of MAP > 65-70 mm Hg so that a dose adjustment, if needed occurs automatically.

2.3.2.2 Pediatric Patients

Studies were conducted in children with post-cardiotomy shock and septic shock. As in adults the children received open-label catecholamines prior to and during the infusions with AVP. The infusion rates of AVP in the children were the adult doses normalized for body weight. Among the hemodynamic variables only the effect of AVP on MAP was consistently reported in the 4 studies conducted in children.

Post-cardiotomy Shock

The studies in post-cardiotomy shock included the open-label studies by Rosenzweig et al and Lechner et al (55,56). Both studies used AVP Pitressin® (Parke-Davis).

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The effect of AVP on MAP in the pediatric population with post-cardiotomy shock is shown in the below table:

Table 12. Mean Initial and Up-titrated Doses of AVP and Change from Baseline in Mean Arterial Blood Pressure 1-2 h after Initiation of AVP Infusions in Children with Post-cardiotomy Shock

Study	**n[a]**	**Age**	**Rate**		**ΔMAP[b]**
			mU/kg/min		**mm Hg**
OL[c]			**Initial**	**Up-titrated**	
Rosenzweig (53)	11[c]	3days-15 years		0.30-2.0[d]	14
Lechner (54)	17	3-12 days	0.10[e]	0.30[e]	20[f]

[a] patients receiving AVP [b] baseline corrected mean arterial blood pressure [c] only n=9 with post-cardiotomy shock considered [d] range [e] median [f] systolic blood pressure

AVP in both studies increased baseline corrected MAP significantly.

Septic Shock

The 2 studies included the randomized, double-blind controlled study by Choong et al and the open-label study by Meyer et al. Both studies used AVP. However, the manufacturer of the drug product was not indicated in the publications.

In the 2 studies conducted in children with septic shock AVP increased baseline corrected MAP significantly as shown in the below table:

Table 13. Mean Initial and Up-titrated Doses of AVP and Change from Baseline in Mean Arterial Blood Pressure 1-2 h after Initiation of AVP Infusions in Children with Septic Shock

Study	**n[a]**	**Age**	**Rate**		**ΔMAP[b]**		**Δ ΔMAP[c]**
			mU/kg/min		**mm Hg**		**mm Hg**
			Initial	**Up-titrated**			
RDBPC[d]					**AVP**	**Placebo**	**AVP**

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Choong [e] (55)	35	4-14 years	0.50	2.0	14	5	9
OL[g]							
Meyer (56)	3	5-6 weeks	ni	4.5	8	na	na

[a] number of patients receiving AVP [b] baseline corrected mean arterial blood pressure [c] baseline and active control corrected mean arterial blood pressure [d] median [e] randomized, double-blind, placebo controlled study [f] 69% of subjects with septic shock and 9% with post-cardiotomy shock [g] open-label study [h] extremely low birth weight ni= not indicated na=not applicable

Of note, the study by Choong et al showed a trend for increased mortality in the subjects receiving AVP (n=10) compared to placebo (n=5). It is unclear whether vasopressin or progression of the disease is causal for the increased mortality in the active treatment group.

AVP and vasopressin increased MAP in the 4 studies in children of all age categories with vasodilatory shock indicating a consistent pressor effect when body weight normalized adult infusion rates are used. The safety database in the children is scarce. No information is available on the pharmacokinetics and the dose- or exposure-response relationship of AVP in children. AVP is not recommended for use in children in post-cardiotomy or septic shock.

2.3.2.3 Race

No information on the impact of race on exposure or response to exogenous AVP is available. However, this is not of concern, AVP is titrated to target effect of MAP >65-70 mm Hg so that a dose adjustment, if needed, occurs automatically.

2.3.2.4 Renal Impairment

No valid information on the impact of different degrees of renal impairment on exposure and response to exogenous AVP is available from the literature. The pre-dialysis mean (SEM) concentrations of endogenous AVP in patients with ESRD [21.3(1.9) pg/mL] are significantly greater than in healthy controls [2.2(0.7) pg/mL] suggesting impaired disposition of endogenous and thus exogenous AVP in patients with ESRD (48). However, a potential increase of the exposure to AVP is not a concern in patients with impaired renal function. AVP is titrated to target effect of MAP > 65-70 mm Hg so that a dose adjustment, if needed, automatically occurs.

2.3.2.5 Hepatic Impairment

No published data on the impact of liver impairment on exposure and response to AVP is available. However, a publication investigating the hemodynamic effect of the AVP

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analogue, 8- L-lysine vasopressin (LVP), infused at a rate of 0.4 U/min into 7 cirrhotic patients (Child-Pugh Class A-C) and 6 matched controls showed a significant prolongation of the pressor and HR effects of AVP in the cirrhotics (57). Given the likelihood that AVP and LVP are metabolized by the same enzymes, the results of this study may be extrapolated to AVP. The sustained pressor effect in the cirrhotic patients suggests prolonged arteriolar vasoconstriction by LVP caused by a reduced clearance. However, a potential increase of the exposure to AVP is not a concern in patients with impaired hepatic function. AVP is titrated to the target effect of MAP > 65-70 mm Hg so that a dose adjustment, if needed, automatically occurs.

2.3.3 What pregnancy and lactation use information is there in the label?

During pregnancy the mean CL of exogenous AVP increases gradually in the second trimester and reaches a peak in the third trimester with 38 mL/kg/min which is about 4 times the preconception value (39, 40). Within 8-12 weeks postpartum the CL is reduced to values seen before conception. The rise of the CL during pregnancy appears to be caused by a significant augmentation of the circulating levels of vasopressinase, a cystine-aminopeptidase, produced by the placenta whose mass increases substantially during pregnancy. The respective time courses of the vasopressinase plasma levels and the trophoplastic mass of the placenta and the CL of AVP during the course of a pregnancy run parallel. The similarity of the respective baseline concentrations of endogenous AVP in the tested females before, during and after pregnancy suggests that the increase in CL is compensated by increased production and subsequent release of endogenous AVP from the pool in the posterior pituitary.

A dose adjustment of AVP in women pregnant up to 11 weeks with vasodilatory shock is not necessary. However, in women pregnant for 12-21 weeks the dose of AVP should be increased 2 fold. In women pregnant ≥ 22 weeks the dose of AVP should be increased 4 fold.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.4.2 What are the drug-drug interactions?

Quantitative Information on Impact of Other Drugs on Exogenous AVP Available

Co-Administered Drugs

The below tables summarize the findings of the drug interaction studies conducted with AVP:

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Table 14. Impact on PK of Exogenous AVP in Healthy Subjects

Impacting Drug	Δ PK of AVP[a]
Estradiol[b] + leuprolide[c] vs leuprolide	0.7 x Css[d]
Halothane, morphine, fentanyl, alfentanyl, sufentanyl	1.0 x Css [e]

[a] ratio of steady-state concentrations in presence and absence of other drug [b] 0.2 mg/day transdermal [c] 0.5 mg/day subcutaneously [d] exogenous AVP [e] endogenous AVP in patients undergoing cardiotomy

Table 15. Impact on PD of Exogenous AVP in Healthy Subjects

Impacting Drug	Δ PD of AVP[a]
Na+ 250 meq/day to 10 mEq/day po	0.5 x CLosm, 0.5 x urine flow
Furosemide 40 mg iv	4 x CLosm, 9 x urine flow
Atrial natriuretic peptide, 20 or 40 µg/h iv	0.6 x CLosm, 0.6 x urine flow
Indomethacin 75 mg po 12 and 3 h prior to AVP	≥ 2 x time to offset of effect on SVR and CI
Tetra-ethylammonium 350 mg iv	1.2 x MAP

[a] ratio of PD parameters in presence and absence of other drug

The results indicate that co-administration of estradiol, tetra-ethylammonium and possibly other ganglionic blocking agents and indomethacin could impact the pressor effect of AVP. However this is not a concern, because AVP is titrated to the target effect > 65-70 mm Hg.

Semi-quantitative Information* on *Impact of Other Drugs on Exogenous AVP Available

1. Catecholamines

It is reasonable to expect a synergistic pressor effect of catecholamines and AVP when co-administered. However, there is no information available on whether the interaction is supra-additive, additive or infra-additive in patients with vasodilatory shock.

2. Drugs Suspected of Inducing the Syndrome of Inappropriate Secretion of the Antidiuretic Hormone (SIADH) or Diabetes Insipidus (60)

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Evidence exists suggesting that the below listed drugs, namely SIADH- and diabetes insipidus inducing drugs, can alter the exposure or the pressor response to endogenous AVP:

Table 16. Drugs Potentially Inducing SIADH

Selective serotonin reuptake inhibitors, tricyclic antidepressants, haloperidol, chlorpropamide, clonidine, enalapril, methyldopa, felbamate, pentamidine, vinblastine, vincristine, ifosphamide, cyclophosphamide

Table 17. Drugs Potentially Inducing Diabetes Insipidus

Lithium, foscarnet, clozapine, demeclocycline

The mechanisms of action involved in the interactions of drugs with the potential of inducing SIADH and diabetes insipidus are not well understood. For these drugs only interactions impacting the V_2-receptor mediated signal pathways are known. Theoretically, the mechanism of action for both groups of drugs could be to change the exposure or the response to endogenous and exogenous AVP. If the mechanism of action of a SIADH inducing drug is an increase in exposure to endogenous AVP, an increase in the exposure to exogenous AVP with increased anti-diuretic- and pressor effects is expected. If a SIADH inducing drug interacts with the V_2-recptor initiated signaling pathway in the kidney, only an increase of the anti-diuretic effect by exogenous AVP is expected with no change in the pressor effect. However, if a SIADH inducing drug interacts also with the V_1-receptor initiated signaling pathway increased pressor- and antidiuretic effects are anticipated. Analogously, opposite changes on the effects of exogenous AVP are expected when diabetes insipidus inducing drugs are co-administered. Dose adjustments of AVP in the presence of SIADH- or diabetes insipidus inducing drugs are not necessary, because AVP is up-titrated to the target MAP > 65-70 mm Hg.

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes. AVP is an agonist of V_1-receptors. Therefore, antagonists and other agonists of this receptor could impact the effect of AVP when co-administered.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

AVP is metabolized by peptidases, proteases and disulfide oxido-reductases. No information on the metabolism of AVP by Cytochrome P450 enzymes is available. It is not likely that AVP is metabolized by CYPs to a significant extent. Therefore, no genetic impact on the metabolism of AVP is expected.

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2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

No published information is available on this subject.

2.4.2.4 Is the drug an inhibitor and/or an inducer of P-gp transport processes?

No published information is available on this subject.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

There is no information available suggesting that metabolic pathways other than those covered in Section 2.4.2.2 are important for AVP. There is no information at hand suggesting that AVP is a substrate, inhibitor or inducer of enzymes or transporters.

2.4.2.6 Does the label specify co-administration of another drug?

Yes. Catecholamines.

2.4.2.7 What other co-medications are likely to be administered to the target population?

Dobutamine, milrinone, corticosteroids, antibiotics

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Yes. See Section 2.4.2

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

Yes. AVP is a V_1-receptor agonist. Therefore, co-administered drugs that are antagonists or agonists of the V_1-receptors or interfer with the signaling pathway are expected to affect the response to AVP.

2.4.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

Yes. The published results on the plasma protein binding of AVP are controversial and no definitive conclusion regarding the extent of the plasma protein binding of AVP can be drawn.

2.4.11 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

The diluent used for diluting AVP prior to infusion is not stated in most of the publications reporting on clinical trials. The stability of AVP was tested by the sponsor in only 2 diluents: isosaline and 5% dextrose. AVP was found to be stable in isosaline. However, when dissolved in 5% dextrose AVP was unstable. The reason for the instability of AVP in 5% dextrose is not known. There is a need to determine the stability of AVP in additional diluents such as, Ringer's, lactated Ringer's, sodium citrate and

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Plasma-Lyte® in order to exclude the possibility that degradation of AVP occurred in the published trials that did not state the diluents used.

2.5 General Biopharmaceutics

NA. AVP is administered by the intravenous route

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the biological fluids?

Plasma and urine concentrations of exogenous AVP were measured by RIA.

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2.6.2 Which metabolites have been selected for analysis and why?

No metabolites were measured. Considering the cleavage sites of the enzymes at AVP, the metabolites are unlikely to be active. However, the metabolites have the potential to interfere with non-specific assay methods.

2.6.3 For all moieties measured, is free, bound, or total measured?

Total plasma concentrations of endogenous and exogenous AVP were measured

2.6.4 What bioanalytical methods are used to assess concentrations?

Radio-immunoassays (RIA) and bioassays were used by the publications to measure plasma concentrations and amounts excreted in urine of unchanged AVP after intravenous infusions. The bioassays developed in the 1960s did not meet the stipulations of the FDA Guidance on Bioanalytical Method Validation of 2001. The more reliable RIA methods developed after 1984 only fulfilled part of the regulatory requirements and they cannot be considered validated. Major deficiencies include that the concentration range of the calibration curve with LLOQ and ULOQ was not reported, a possible interference from metabolites of AVP was not tested and QC samples were not measured along samples with unknown concentrations. The accepted RIA methods reported on the lower limit of sensitivity and intra- and inter-assay coefficients of variation, the extraction method of AVP from plasma, the recovery of AVP from spiked plasma, the cross-reactivity with LVP, oxytocin and vasotocin and the measures taken to ensure stability of AVP after sample collection until and during assaying. An additional acceptance criterion applied by the Reviewer was to consider only studies administering synthetic AVP Pitressin® (Parke-Davis).

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2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What is curve fitting technique?

As stated in 2.6.4 the range of the standard curve was not reported. Also, the curve fitting techniques were not stated in the publications.

2.6.4.2 What are the lower and upper limits of quantitation?

The LLOQ and ULOQ values were not reported.

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

Accuracy and precision of the different RIAs at LLOQ and ULOQ were not reported.

2.6.4.4 What is the sample stability under conditions used in the study?

Stability of the study samples was not tested with the rigor required by the FDA Guidance on Bioanalytical Method Validation of 2001.

2.6.4.5 What is the QC sample plan?

See 2.6.4

3. References

1. Holmes CL, Landry DW, Granton TJ. Science Review: Vasopressin and the Cardiovascular System Part 1-Receptor Physiology. Crit Care 2003;7:427-434

2. Reilly RF and Jackson EK. In: Goodman and Gilman's Clinical Pharmacology Basis of Therapeutics, 12e, Ed: Brunton LL, Chabner BA, Knollmann BC

3. Moehring J, Glaenzer K, Maciel A, Jr., Duesing R, Kramer HJ, Arbogast R, Koch-Weser J. Greatly Enhanced Pressor Response to Antidiuretic Hormone in Patients with Impaired Cardiovascular Reflexes Due to Idiopathic Orthostatic Hypotension. J Cardiovasc Pharmacol 1980;2:367-376

4. Glaenzer K, Pruessing B, Duesing R, Kramer HJ. Hemodynamic and Hormonal Responses to 8- Arginine-Vasopressin I Healthy Man: Effects of Indomethacin. Klin Wochenschrift1982;60: 1234-1239

5. Wagner HM, Braunwald E. The Pressor Effect of the Antidiuretic Principle of the Posterior Pituitary in Orthostatic Hypotension J Clin Invest 1956;35: 1412-1418

6. Aylward PE, Floras JS, Leimbach WN, Abboud FM. Effects of Vasopressin in the Circulation and Its Baroreceptor Reflex in Men. Circulation 1986;73:1145-1154

Reference ID: 3313873

7.Suzuki S, Takeshita A, Imaizumi T, Hirooka Y, Yoshida M, Ando S, NakamuraM. Biphasic Forearm Vascular Responses to Intra-arterial Arginine Vasopressin J Clin Invest 1989; 84:427-434

8. Hirsch AT, Dzau VJ, Majzoub, JA, Creager MA. Vasopressin-Mediated Forearm Vasodilation in Normal Humans. Evidence for a Vascular Vasopressin V_2 Receptor. J Clin Invest 1989;84:418-426

9. Argenziano M, Choudri AF, Oz MC, Rose EA, Smith CR, Landry DW. A Prospective Randomized Trial of Arginine Vasopressin in the Treatment of Vasodilatory Shock after Left Ventricular Assist Device Placement. Circulation 1997;96:II286-II290.

10. Argenziano M, Chen JM, Choudri AF, Cullinane S, Garfein E, Weinberg AD, Smith CR Jr, Rose EAA, Landry DW, Oz MC. Management of Vasodilatory Shock after Cardiac Surgery: Identification of Predisposing Factors and Use of a Novel Pressor Agent. J Thorac Cardiovasc Surg 1998;116:973-980

11. Argenziano M, Chen JM, Cullinane S, Choufri AF, Rose EA, Smith CR, Edwards NM, Landry DW, Oz MC. Arginine Vasopressin in the Management of Vasodilatory Hypotension after Cardiac Transplantation J Heart Lung Transplant 1999;18:814-817

12. Morales DLS, Gregg D, Helman DN, Williams MR, Naka Y, Landry DW, Oz MC. Arginine Vasopressin in the Treatment of 50 Patients with Post-cardiotomy Vasodilatory Shock. Ann Thorac Surg 2000;69:102-106

13. Duenser MW, Mayr R, Stallinger A, Ulmer H, Ritsch N, Knotzer H, Pajk W, Mutz NJ, Hasibeder WR. Cardiac Performance During Vasopressin Infusion in Post-cardiotomy Shock. Intensive Care Med2002; 28:746-751

14. Luckner G, Duenser MW, Stadlbauer K-H, Mayr VD, Jochberger S, Wenzel V, Ulmer H, Pajk W, Hasibeder WR, Friesenecker B, Knotzer H. Cutaneous Vascular Reactivity and Flow Motion Response to Vasopressin in Advanced Vasodilatory Shock and Severe Post-Operative Multiple Organ Dysfunction Syndrome. Critical Care 2006;10: R40

15. Malay MB. Ashton RC, Jr, Landry DW, Townsend RN. Low Dose Vasopressin in the Treatment of Vasodilatory Septic Shock. J Trauma 1999;47:6999-705

16. Patel BM, Chittock DR, Russell JA. Beneficial Effects of Short Term Vasopressin Infusion During Severe Septic Shock. Anestesiology 2002: 96; 576-582

17. Russell JA, Walley KR, Singer J, Gordon AC, Hebert PC, Cooper JD, Holmes CL, Mehta S, Granton JT, Storms MM, Cook DJ, Presneill JJ, Ayers D. Vasopressin versus

Reference ID: 3313873

Norepinephrine Infusion in Patients with Septic Shock. N Engl J Med 2008;358:877-887 and Supplementary Appendix

18. Lauzier F, Levy B, Lamarre P, Lesur O. Vasopressin or Norepinephrine in Early Hyperdynamic Septic Shock: A Randomized Clinical Trial. Intensive Care Med 2006;32:1782-1789

19. Landry DW, Levin HR, Gallant EM, Ashton RC, Jr, Seo S, D'Allessandro. Oz MC, Oliver JA. Vasopressin Deficiency Contributes to the Vasodilation of Septic Shock. Circulation 1997;95:1122-1125

20. Lam SW, Bauer SR, Cha SS, Oyen LJ. Lack of an Effect of Body Mass on the Hemodynamics Response to Arginine Vasopressin During Septic Shock. Pharmacotherapy 2008;28:591-599

21. Duenser MW, Mayr AJ, Ulmer H, Knotzer H, Sumann G, Pajk W, Friesenecker B, Hasibeder WR. Arginine Vasopressin in Advanced Vasodilatory Shock. A Prospective, Randomized, Controlled Study. Circulation 2003;107:2313-1219

22. Luckner G, Duenser MW, Jochberger S, Mayr VD, Wenzel V, Ulmer H, Schmid S, Knotzer H, Pajk W, Hasibeder WR, Mayr AJ, Friesenecker B. Arginine Vasopressin in 316 patients with Advanced Vasodilatory Shock. Crit Care Med 2005;33:2659-2666

23. Luckner G, Mayr VD, Jochberger S, Wenzel V, Ulmer H, Hasibeder WR, Duenser MW. Comparison of Two Dose Regimens of Arginine Vasopressin in Advanced Vasodilatory Shock. Crit Care Med 2007;35:2280-2285

24. Nygren A, Thoren A, Ricksten S-E. Vasopressin Decreases Intestinal Mucosal Perfusion: A Clinical Study on Cardiac Surgery Patients in Vasodilatory Shock. Acta Anesthesiol Scand 2009;53:581-588

25. Torgersen C, Duenser MW, Wenzel V, Jochberger S, Mayr VD, Schmittinger CA, Lorenz I, Schmid S, Westohal M, Grander W, Luckner G. Comparing two different Arginine-Vasopressin Doses in Advanced Vasodilatory Shock: A Randomized, Controlled, Open-Label Trial. Intensive Care Med 2010;36:57-65

26. Morales DLS, Garrido MJ, Madigan JD, Helman DN, Faber J, Williams MR, Landry DW, Oz MC. A Double-Blind Randomized Trial: Prophylactic Vasopressin Reduces Hypotension after Cardiopulmonary Bypass. Ann Thorac Surg 2003;75: 926-930

27. Papadopoulos G, Sintou E, Siminelakis S, Koletsis E, Baikoussis N, Apostolakis E. Perioperative Infusion of Low-Dose of Vasopressin for Prevention and Management of Vasodilatory Vasoplegic Syndrome in Patients Undergoing Coronary Artery Bypass Grafting-A Double-Blind Randomized Study. J Cardiothorac Surg 2010; 51-12

Reference ID: 3313873

28. Hasija S, Makhija N, Choudhury M, Hote M, Chauhan S, Kiran U. Prophylactic Vasopressin in Patients Receiving the Angiotensin-Converting Inhibitor Ramipril Undergoing Coronary Artery Bypass Graft Surgery. J Cardiothorac Vasc Anesth 2010; 24: 230-238

29. Duenser MW, Hasibeder WR, Wenzel V, Schwarz S, Ulmer H, Knotzer H, Pajk W, Friesenecker BE,Mayr AJ. Endocrinologic Response to Vasopressin Infusion in Advanced Vasodilatory Shock. Crit Care Med 2004;'32:1266-1271

30. Erfurth EM, Hedner P, Lundin S, Ekman R. Release of Prolactin as well as Adrenocorticotropin after Administration of Arginin-Vasopressin to Healthy Men. Horm Metab Res 1996;28: 5099-602

31. Hensen J, Hader O, Baehr V, Oelkers W. Effects of Incremental Infusions of Arginine Vasopressin on Adrenocorticopin and Cortisol Secretion in Man. J Clin Endocrinol Metab 1988; 66: 668-671

32. Klinzing S, Simon M, Reinhart K, Bredle DL, Meier-Hellmann A. High-Dose Vasopressin is not Superior to Norepinephrine in Septic Shock. Crit Care Med 2003;31:2646-2650

33. Fornaro R, Ferraris R, Belcastro E, Parodi G. Impiego Della Vasopressina Nel Trattamento Delle Varici Esofagee Sanguinanti. Minerva Medica 1985;761719-1726

34. Mauro VF, Bingle JF, Ginn SM, Jafri FM. Torsades de Pointes in a Patient Receiving Intravenous Vasopressin. Crit Care Med 1988;16:200-201

35. Kupferschmidt H, Meier CH, Sulzer M, Meier PJ, Buehler H. Bardycardie und Ventrikulaere Tachycardies vom Typ Torsades de Pointes als Nebenwirkung von Vasopressin: 3 Fallberichte. Praxis 1996;85:340343

36. Kelly KJ, Stang JM, Mekhjian HS. Vasopressin Provocation of Ventricular Dysrhythmia. Ann int Med 1980;92:205-206.

37. Moses AM, Steciak E. Urinary and Metabolic Clearance of Arginine Vasopressin in Normal Subjects. Am J Physiol 251 1986;20:R365-370

38. Moses AM, Jones C, Yucha CB. Effects of Sodium Intake, Furosemide, and Infusion of Atrial Natriuretic Peptide on the Urinary and Metabolic Clearances of Arginine Vasopressin in Normal Subjects. J Clin Endocrinol Metab 1990;70:222-229

39. Davison JM, Sheills EA, Barron WM, Robinson AG, Lindheimer MD. Changes in the Metabolic Clearance of Vasopressin and in Plasma Vasopressinase throughout Human Pregnancy. J Clin Invest 1989;83:1313-1318

Reference ID: 3313873

40. Davison JM, Sheills EA, Philips PR, Barron WM, Lindheimer MD. Metabolic Clearance of Vasopressin and a Analogue Resistant to Vasopressinase in Human Pregnancy. Am J Physiol 1993; 264:F348-F353

41. Stachenfeld NS, Taylor HS, Leone CA, Keffe DL. Oestrogen Effects on Urine Concentrating Response in Young Women. J Physiol 2003;552:869-880

42. Kimura T, Matsui K, Ota K, Yoshinaga K. Radioimmunoassay of Arginine Vasopressin in Human Plasma and Urine, a Resin Microcolumn Method. Tohoku J exp Med 1980;131: 37-46

43. Sakurai H, Kurimoto F, Ohono H, Kanai A, Nomura K, Demura H, Shizume K. A simple and sensitive radioimmunoassay for 8-arginine vasopressin in human plasma using reversed phase C18 silica column. Folia endocrinologica 1985;61: 724-736

44. Freund BJ, Shizuru EM, Hashiro GM, Claybaugh JR. Hormonal, Electrolyte, and Renal Responses to Exercise are Intensity Dependent. J Appl Physiol 1991;70:900-906

45. Jochberger S, Mayr VD, Luckner G, Wenzel V, Ulmer H, Schmid S, Knotzer H, Pajk W, Hasibeder W, Friesenecker B, Mayr AJ, Duenser MW. Serum Vasopressin Concentrations in Critically Ill Patients. Crit Care Med 2006;34:293-299

46. Saztalowicz VL, Goldberg JP, Anderson RJ. Plasma Antidiuretic Hormone in Acute Respiratory Failure. J Am Med 1982;72: 583-587

47. Philbin DM, Coggins CH, Emerson CW, Levine FH, Buckley MJ. Plasma vasopressin levels and urinary sodium excretion during cardiopulmonary bypass. J Thorac Cardiovasc Surg 1979;77:582-585

48. Iitake K, Kimura T, Matsui K, Ota K, Shoji M, Inoue M, Yoshinaga K. Effect of hemodialysis on plasma ADH levels, plasma renin activity and plasma aldosterone levels in patients with end-stage renal disease. Acta Endocrinol 1985;110:207-213

49. Baumann G, Dingman JF. Distribution, Blood Transport, and Degradation of Antidiuretic Hormone in Man. J Clin Invest 1976; 57:1109-1116

50. Claybaugh JR, Uyehara CFT. Metabolism of Neurohypophysal Hormones. Ann NY Acad Sci 1993;689:250-268

51. Share L, Kimura T, Matsui K, Shade RE, Crofton JT. Metabolism of Vasopressin Federation Proc 1985; 44:59-61

52. Carone FA, Christensen EI, Flouret G. Degradation and Transport of AVP by Proximal Tubule. Am J Physiol 1987; 253:F1120-1128

Reference ID: 3313873

53. Choong, K, Bohn D, Fraser DD, Gaboury I, Hutchinson JS, Joffe AR, Litalien C, Menon K, McNamara P, Ward RE, on Behalf of the Canadian Critical Care Trials Group. Vasopressin in Pediatric Vasodilatory Shock. A Multi-Center Randomized, Controlled Study. Am J Respir Crit Care Med2009;180:632-639

54. Meyer S, Gottschling S, Baghai A, Wurm D, Gortner L. Arginine-vasopressin in Catecholamine-Refractory Septic Versus Non-septic Shock in Extremely Low Birth Weight Infants with Acute Renal Injury Crit Care 2006;10:R71

55. Rosenzweig EB, Starc TJ, Chen JM, Cullinane S, Timchak DM, Gersony WM, Landry DW, Galantowicz, ME. Intravenous Arginine-Vasopressin in Children with Vasodilatory Shock after Cardiac Surgery. Circulation 1999; 100: Suppl II: II182-186

56. Lechner E, Hofer A, Mair R, Moosbauer W, Sames E,-Dolzer, Tulzer G. Arginine-Vasopressin in Neonates with Vasodilatory Shock after Cardiopulmonary Bypass. Eur J Pediatr 2007:166:1221-1227

57. Moreau R, Hadengue A, Soupison T, Mechin G, Assous M, Roche-Sicot J, Sicot C. Abnormal Pressor Response to Vasopressin in Patients with Cirrhosis: Evidence for Impaired Buffering Mechanism. Hepatology 1990;12: 7-12

58. Philbin DM, Coggins CH. Plasmma Antidiuretic Hormone Levels in Cardiac Surgical Patients during Morphine and Halothane Anesthesia. Anesthesiology1978;49:95-98

59. De Lange S, Boscoe MJ, Stanley TH, de Brujin N, Philbin DM, Coggins CH. Antidiuretic and Growth Hormone Responses during Coronary Artery Surgery with Sufentanil-Oxygen and Alfentanil-Oxygen Anesthesia in Man. Anesth Analg 1982;61:434-438

60. Goodman & Gilman’s The Pharmacological Basis of Therapeutics, 12e 2013

Reference ID: 3313873

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/s/

PETER HINDERLING
05/24/2013

RAJANIKANTH MADABUSHI
05/24/2013

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204485	**Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	September 26, 2012		
Division:	Division of Cardiovascular and Renal Products	**Team Leader:** Angelica Dorantes, PhD	
Applicant:	JHP Pharmaceuticals LLC	**Acting Supervisor:** Richard Lostritto, PhD	
Trade Name:	TBD	**Date Assigned:**	October 2, 2012
Established Name:	Vasopressin Injection, USP	**Date of Review:**	March 15, 2013
Indication:	For the treatment of vasodilatory shock	**Type of Submission:** Original New Drug Application – 505(b)(2)	
Dosage form/ strengths	Solution for Injection/ 20 Units/mL		
Route of Administration	IV Injection		

SUBMISSION:

Background: The proposed drug product is a sterile solution for injection containing synthetic vasopressin (20 U/mL) intended to be administered as an infusion via the intravenous (IV) route of administration. Arginine vasopressin (AVP), also called vasopressin, is a stress hormone with vasoactive and antidiuretic properties. The proposed drug product is a currently marketed unapproved drug product. This application is an electronic NDA, filed as a 505(b)(2) application in which the Applicant relies solely on published literature to support the safety and efficacy of the proposed drug product.

Review: This Biopharmaceutics review is being focused on the evaluation of the differences between the proposed drug product formulation and the formulations of the drug products used in the published literature.

BIOPHARMACEUTICS INFORMATION:

The Applicant is requesting a waiver of the requirement to provide evidence of in-vivo bioavailability based on 21CFR §320.22(d)(2). However, a Biowaiver does not apply to this NDA, because the Applicant has provided evidence of in-vivo bioavailability using published literature. The pharmacokinetic (PK) information in the published literature will be reviewed by the Office of Clinical Pharmacology (OCP) reviewer.

Reference ID: 3277472

COMPARISON OF THE FORMULATIONS OF THE PROPOSED DRUG PRODUCT AND THE DRUG PRODUCTS USED IN THE PUBLISHED LITERATURE:

The 4 main publications supporting the efficacy, safety and PK information are:

- Argenziano M., 1997: A prospective randomized trial of Arginine vasopressin in the treatment of vasodilatory shock after left ventricular assist device placement.
- Malay B., 1999: Low-dose vasopressin in the treatment of vasodilatory septic shock.
- Patel BM., 2002: Beneficial effects of short-term vasopressin infusion during severe septic shock.
- Russell JA., 2008: Vasopressin versus norepinephrine infusion in patients with septic shock.

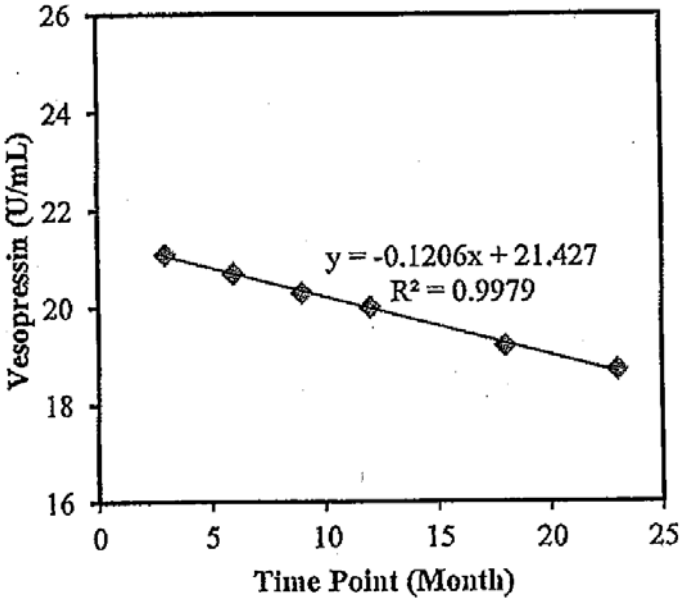
Numerous other publications were provided to support this NDA.
The Argenziano and the Malay publications used Pitressin Injection, USP from Parke-Davis. The currently marketed unapproved drug product formulation (manufactured by JHP) is the same as the Parke-Davis formulation and can be compared to the proposed formulation as follows:

Ingredient	Function	Proposed formulation (amount/mL)	Currently marketed (unapproved) JHP Pitrissin formulation - Parke-Davis formulation (amount/mL)
Vasopressin, USP	Active Ingredient	20 Units	(b) (4)
Chlorobutanol, NF	Preservative	(b) (4)	
Acetic acid, NF	pH adjustment	QS to pH 3.4-3.6	QS to pH 3.6
Water for Injection, USP	Diluent	(b) (4)	

The currently marketed formulation contains a (b) (4) overage (b) (4). The currently marketed formulation conforms to the USP monograph for Vasopressin Injection that requires the drug product potency to be between 90.0% and 110.0% of label claim. The overage was added to (b) (4) however, the Applicant was advised by FDA during a pre-NDA meeting held on October 17, 2011 to manufacture "no–overage" registration batches to support the filing of a NDA.

Reference ID: 3277472

Typical drug product degradation observed in the currently marketed formulation upon storage at 25 °C, 60% RH:



The currently marketed drug product has an expiry date of 24 months, during which it conforms to the USP monograph requirements of 18.0 – 22.0 U/mL for vasopressin potency. The articles in the published literature do not specify how long the drug product has been stored before it was used in the clinical trials, however, based on the above figure, it is expected that the vasopressin concentration was between 18.5 and 21.5 U/mL, and on average the vasopressin concentration was around 20±1.5 U/mL. Vasopressin Injection, USP formulations from other sources used in other publications are not known, however, these formulations should have a vasopressin concentration between 18.0 and 22.0 U/mL.

In conclusion, the proposed vasopressin concentration of 20 U/mL is comparable to the vasopressin concentration of the drug products used in the published literature. The differences in the amount of preservative in the drug products are not expected to affect the bioavailability of vasopressin via the IV route of administration. The pH of the formulation is critical because at pHs below 3.4 and above 3.6, degradation of vasopressin accelerates, with the degradation rate increasing as the pH deviates further from the pH 3.4-3.6 range. In addition, the vasopressin drug product is diluted in a diluent and administered as an infusion. Several published articles indicate that 5% dextrose or saline (0.9% NaCl) were used as a diluents.

Per the proposed label, the use of 5% dextrose is not allowed for the proposed drug product due to degradation of vasopressin in the presence of dextrose. Therefore the concentration of vasopressin in the infusion solution, used during clinical studies in the published articles using 5% dextrose as the diluent, was likely much lower than the calculated value based on the label claim. The concern about the administered dose is partly compensated by the fact that the vasopressin dose is titrated to maintain the mean arterial pressure (MAP) at 60-75 mm Hg, so that any vasopressin degradation will be compensated by a higher modified dose.

Reference ID: 3277472

RECOMMENDATION:

The Applicant's request for a waiver of the requirement to provide evidence of in-vivo bioavailability based on 21CFR §320.22(d)(2) does not apply to this NDA. The provided pharmacokinetic information from the published literature is being used to satisfy the CFR requirement to characterize the pharmacokinetics (bioavailability) of the proposed product.

Comparison of the proposed drug product formulation to those formulations used in the published literature, indicate that the formulation and concentration of vasopressin for each one of the products used in these references is not significantly different from that of the proposed product. The expiry date for the proposed drug product should be set, so that the vasopressin concentration will not drop below 18 U/mL, in order to be comparable to the drug products used in the published literature, and also in order to conform to the USP monograph for Vasopressin Injection.

From the Biopharmaceutics perspective, NDA 204485 for Vasopressin Injection, USP (20 U/mL) is recommended for **APPROVAL**.

Signature	**Signature**
Elsbeth Chikhale, Ph.D.	Angelica Dorantes, Ph.D.
Biopharmaceutics Reviewer	Biopharmaceutics Team Leader
Office of New Drug Quality Assessment	Office of New Drug Quality Assessment

cc NDA 204485/DARRTS/ RLostritto

Reference ID: 3277472

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/s/

ELSBETH G CHIKHALE
03/15/2013

ANGELICA DORANTES
03/15/2013

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	204485
Submission Date	9/26/12
Product name, generic name of the active	Pitressin (vasopressin) Injection
Dosage form and strength	Solution for Injection – 20 units per mL
Route of Administration	IV infusion
Applicant	JHP Pharmaceuticals LLC
Clinical Division	Division of Cardiovascular and Renal Products
Type of Submission	Original NDA – 505(b)(2)
Biopharmaceutics Reviewer	Elsbeth Chikhale, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING

	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?		x	NA
2.	Is the dissolution test part of the DP specifications?		x	NA
3.	Does the application contain the dissolution method development report?		x	NA
4.	Is there a validation package for the analytical method and dissolution methodology?		x	NA
5.	Does the application include a biowaiver request?	x		Section 1.12 The Applicant is requesting a biowaiver based on 21 CFR 320.22(d)(2).
6.	Does the application include an IVIVC model?		x	
7.	Is information such as BCS classification mentioned, and supportive data provided?		x	
8.	Is information on mixing the product with foods or liquids included?		x	
9.	Is there any in *vivo* BA or BE information in the submission?		x	This is a literature based NDA. The PK information included in the published references will be evaluated by the Office of Clinical Pharmacology.

Reference ID: 3214593

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
10.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
11.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
12.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
13.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		x	

The proposed drug product is a currently marketed unapproved drug product. The NDA contains published literature references in lieu of clinical studies.

{See appended electronic signature page}

Elsbeth Chikhale, Ph.D. — 11/8/12
Biopharmaceutics Reviewer — Date
Office of New Drug Quality Assessment

{See appended electronic signature page}

Angelica Dorantes, Ph.D. — 11/8/12
Biopharmaceutics Team Leader — Date
Office of New Drug Quality Assessment

Reference ID: 3214593

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/s/

ELSBETH G CHIKHALE
11/08/2012

ANGELICA DORANTES
11/08/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**204 485**	**Brand Name**	**Pitressin®**
OCP Division (I, II, III, IV, V)	**I**	**Generic Name**	**Vasopressin Injection USP, Synthetic 8-L-Arginine Vasopressin**
Medical Division	**DCRP**	**Drug Class**	**Posterior Pituitary Hormone, Nonapeptide**
OCP Reviewer	**Peter H. Hinderling, MD**	**Indication(s)**	**Adjuvant treatment in vasodilatory shock to increase blood pressure**
OCP Team Leader	**Raj Madabushi, PhD**	**Dosage Form**	**Intravenous injection**
Pharmacometrics Reviewer	**___**	**Dosing Regimen**	**Intravenous infusion titrated to maintain mean arterial blood pressure (MAP) ≥ 70 mmHg**
Date of Submission	**9-25-2012**	**Route of Administration**	**Intravenous**
Estimated Due Date of OCP Review	**5-25-2013**	**Sponsor**	**JHP Pharmaceuticals**
Medical Division Due Date	**6-25-2013**	**Priority Classification**	**Standard 505(b)(2)**
PDUFA Due Date	**7-25-2013**		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Summary

The endogenous hormone 8-L-arginine-vasopressin (AVP) is formed in the hypothalamus and secreted in the blood stream by the posterior pituitary. AVP is a nonapeptide V_1-,V_2- and V_3-receptor agonist inducing vasoconstriction, antidiuresis, and release of adrenocorticotropine hormone, respectively. In patients with vasodilatory shock AVP promotes primarily vasoconstriction of arterioles. The proposed drug product is a sterile solution for intravenous infusion containing synthetic AVP as the active ingredient (Vasopressin Injection, USP) packaged as 1 mL vial (20 pressor units). Pitressin® Injection (Parke-Davis) under NDA 19286 was approved for prevention and treatment of postoperative abdominal distention, in abdominal roentgenography to dispel interfering gas shadows and in diabetes insipidus. The original Pitressin® was a mixture of lysine vasopressin (porcine) and arginine vasopressin (bovine). Pitressin® contained synthetic 8-L-arginine vasopressin. (b) (4) Parke-Davis withdrew the product from the market.

The clinical pharmacology and clinical efficacy and safety sections of the NDA submitted by JHP Pharmaceuticals consist entirely of publications. The submission makes reference to 77 references. The label is based on information from 13 of these publications. The pharmacokinetic information on AVP in healthy subjects and patients is based on publications from the 1960s-1980s. The information on the pharmacological effects, clinical efficacy and safety are from papers published in the 1980s and 1990s and the first decade of 2000.

The submitted publications in the clinical pharmacology section of the NDA report results on AVP in the following areas:

PK of Vasopressin

Exogenous AVP

Healthy Adult Subjects

- PK parameters after intravenous injection or infusion of synthetic AVP or AVP from an extract of bovine posterior pituitary
- Plasma protein binding
- Metabolism and urine excretion
- Special Population: Pregnancy
- Intrinsic and extrinsic factors

Adult Patients with Target Disease

- Dose-Response
- Pharmacological Effects
- Adverse Events

Children with Target Disease

- Pharmacological Effects

Endogenous AVP

Healthy Subjects

- Plasma levels

APPEARS THIS WAY ON ORIGINAL

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			Partly
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?		X		
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?		X		See below text
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			Titration to MAP ≥ 70 mm Hg
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		X		Clin. Pharmacol information provided is scarce. Because AVP is titrated to MAP, PK and exposure-response information is less critical.
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?		X		There is no need for biopharmaceutic studies. Given the AVP is titrated to MAP paucity of Clin. Pharmacol. information does not prevent approvability
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	No translation needed

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Given that the development of AVP did not follow a drug development plan with feedback from the Agency and studies designed in accordance with FDA Guidances the sponsor should have defined a priori defined acceptance criteria to select the pivotal studies exhibiting scientifically acceptable methods and results. However, this was not done.

A significant number of the submitted publications reporting on the response to administration of exogenous AVP do not provide information on the identity and source of the vasopressin used. A comparison of the publications that indicate identity and source of the vasopressin used show that indeed different vasopressins were injected including natural and synthetic AVP. The doses of the different vasopressins used in the publications are provided for some only in pressor units and for others only in mass units. However, the plasma concentrations of the vasopressins are given in mass units/mL throughout. Thus, with vasopressins for which information on the infusion rate is provided in pressor, clearance cannot be calculated or checked for accuracy. Also, the impact of changes in infusion rate on the PK parameters of the vasopressins cannot be

evaluated. The sponsor should provide this information on the transformation factors to be used to perform the required calculations.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

See above. In addition the sponsor should provide:

1. Acceptance criteria they used when selecting the pivotal studies supporting the indication sought. The Reviewer determined that a significant number of additional, potentially meaningful publications exist which the sponsor did not consider.
2. Information on MW, biopotency and correction factors to be used for calculating mass units from pressor units and vice versa of all vasopressins used in the relevant publications.
3. Information on source and identity of the vasopressins used in the relevant publications.

Peter H. Hinderling, MD	11-8-2012
Reviewing Clinical Pharmacologist	Date
Raj Madabushi, PhD	11-8-2012
Team Leader/Supervisor	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PETER HINDERLING
11/08/2012

RAJANIKANTH MADABUSHI
11/08/2012