Vasopressin Intravenous Infusion Causes Dose Dependent Adverse Cardiovascular Effects in Anesthetized Dogs

Luiz Cláudio Martins, Maricene Sabha, Maria Ondina Paganelli, Otávio Rizzi Coelho, Silvia Elaine Ferreira-Melo, Marcos Mello Moreira, Adriana Camargo de Cavalho, Sebastião Araujo, Heitor Moreno Junior
Faculdade de Ciências Médicas da Universidade Estadual de Campinas - Unicamp - Campinas, SP - Brazil

Abstract
Background: Arginine vasopressin (AVP) has been broadly used in the management of vasodilatory shock. However, there are many concerns regarding its clinical use, especially in high doses, as it can be associated with adverse cardiovascular events.

Objective: To investigate the cardiovascular effects of AVP in continuous IV infusion on hemodynamic parameters in dogs.

Methods: Sixteen healthy mongrel dogs, anesthetized with pentobarbital were intravascularly catheterized, and randomly assigned to: control (saline-placebo; n=8) and AVP (n=8) groups. The study group was infused with AVP for three consecutive 10-minute periods at logarithmically increasing doses (0.01; 0.1 and 1.0U/kg/min), at them 20-min intervals. Heart rate (HR) and intravascular pressures were continuously recorded. Cardiac output was measured by the thermodilution method.

Results: No significant hemodynamic effects were observed during 0.01U/kg/min of AVP infusion, but at higher doses (0.1 and 1.0U/kg/min) a progressive increase in mean arterial pressure (MAP) and systemic vascular resistance index (SVRI) were observed, with a significant decrease in HR and the cardiac index (CI). A significant increase in the pulmonary vascular resistance index (PVRI) was also observed with the 1.0U/kg/min dose, mainly due to the decrease in the CI.

Conclusion: AVP, when administered at doses between 0.1 and 1.0U/kg/min, induced significant increases in MAP and SVRI, with negative inotropic and chronotropic effects in healthy animals. Although these doses are ten to thousand times greater than those routinely used for the management of vasodilatory shock, our data confirm that AVP might be used carefully and under strict hemodynamic monitoring in clinical practice, especially if doses higher than 0.01 U/kg/min are needed. (Arq Bras Cardiol 2010;94(2): 213-218)

Key words: Arginine vasopressin; cardiac output; hemodynamic / drug effects; drug toxicity; dogs.

Introduction
Vasopressin is a neuropeptide consisting of nine amino acids with antidiuretic and vasoconstrictor effects. Its powerful effect on vascular smooth muscle increases blood pressure and systemic vascular resistance. Vasopressin is synthesized in neurons located in paraventricular and suprachiasmatic nuclei of the hypothalamus, and it is stored in the posterior pituitary. There are three types of vasopressin receptors: V₁, V₂, and V₃. Vasopressin V₁ receptors present in blood vessels are responsible for vasoconstriction, vasopressin V₂ receptors present in renal collecting duct cells are mainly responsible for the antidiuretic effects and vasopressin V₃ receptors present in the adenohypophysis are responsible for ACTH secretion.

Vasopressin is essential for cardiovascular homeostasis, acting via the kidney to regulate water reabsorption, on the vasculature to regulate smooth muscle tone, and as a central neurotransmitter, modulating brainstem autonomic function. Although it is massively released in response to stress or shock states, a relative deficiency of vasopressin has been found in prolonged vasodilatory shock, such as is seen in severe sepsis. In this circumstance, exogenous vasopressin has marked pressor effects, even at doses that would not affect blood pressure in healthy individuals. These two findings provide the rationale for the use of vasopressin in the treatment of septic shock.

In the last decade, vasopressin has been broadly used as an adjunct vasopressor agent for the management of catecholamine-resistant vasodilatory shock, and is also recommended to increase peripheral vascular tone during cardiopulmonary resuscitation as an alternative to epinephrine. Despite considerable research attention, the mechanisms for vasopressin deficiency and hypersensitivity in vasodilatory shock remain unclear. Moreover, the clinical experience with vasopressin, as well as its hemodynamic effects, is still under investigation.
Effects in continuous infusions with progressive doses has been limited. For this reason, we investigated the cardiovascular effects of vasopressin on hemodynamic parameters when used as continuous infusion and at progressive doses in anesthetized healthy dogs.

Methods

Ethical aspects: all procedures were approved by our institutional Ethical Animal Care Committee and the experiments were carried out in accordance with the guidelines published by the National Institutes of Health and the European Community Guidelines for use of experimental animals.

Setting: Cardiovascular Pharmacology Laboratory at the Pharmacology Department of the Faculty of Medical Sciences, University of Campinas (UNICAMP), São Paulo, Brazil.

Population: Sixteen adult healthy mongrel dogs, both sexes, weighing 15 ± 1 kg.

Animal handling and experimental model preparation: the animals were prepared as described by Tanus-Santos et al. After a fasting night with free access to water, the animals were anesthetized with a loading dose of sodium pentobarbital (10 mg · kg⁻¹ · IV) and an adequate level of anesthesia was maintained by a continuously IV infusion of the same drug (2-4 mg · kg⁻¹ · h⁻¹). The dogs were tracheally intubated and mechanically ventilated with room air using a volume-cycled respirator (Dual Phase Control Respirator; Harvard Apparatus, Boston, MA, USA). The tidal volume was 15 mL/kg, and the respiratory rate was adjusted to maintain a baseline physiologic PaCO₂ (around 35-40 mmHg, as demonstrated by end-tidal CO₂ monitoring).

A fluid-filled catheter was placed into the left femoral artery for mean arterial pressure (MAP) monitoring, via a pressure transducer (AS-3 Datex-Engstrom, Helsinki, Finland). Another plastic catheter was placed into the left femoral vein for fluid administration. A 7F balloon-tipped Swan-Ganz thermodilution catheter was placed in the pulmonary artery via the right femoral vein, and its correct location was confirmed by detection of typical pressure wave of this artery. The catheter was connected to a pressure transducer (AS-3 Datex-Engstrom, Helsinki, Finland) to allow monitoring of the mean pulmonary artery pressure (MPAP), central venous pressure (CVP), and pulmonary capillary wedge pressure (PCWP). The transducers were zeroed at the level of the right heart and recalibrated before each set of measurements.

Cardiac output was measured in triplicate by a bolus injection of 5 mL of normal saline solution, and the results were recorded and stored in a computerized system (Datex-Engstrom, Helsinki, Finland). Body surface area (BSA) of each dog was calculated according to the following formula: K × BW⁰.⁶⁷ - 100 [where Kₐ for dogs = 10.1; body weight (BW) is measured in kg; and BSA is expressed in m²], and cardiac index (CI), systemic vascular resistance index (SVRI), and pulmonary vascular resistance index (PVRI) were calculated by using standard formulas. Heart rate (HR) was measured using a surface electrocardiogram (lead I).

The experiment: the animals were maintained with a continuous IV infusion of 0.9% NaCl solution (5 mL · kg⁻¹ · h⁻¹) throughout the whole experiment. After the end of the intravenous catheterization procedures, a stabilization period of 20 minutes was observed and baseline (BL) hemodynamic data were firstly recorded. Subsequently, the animals were randomly assigned to two equal groups: CONTROL (saline-placebo; sham-group; n = 8) and VASOPRESSIN (n = 8). The CONTROL group received continuous infusions (20 mL) of 0.9% NaCl for 10 minutes, at 20-minute intervals, for three times. The VASOPRESSIN group was infused with AVP (Arginine Vasopressin- Acetate Salt, Sigma Chemical Co. USA) for three consecutive 10-min periods at logarithmically increasing doses (0.01; 0.1 and 1.0 U/kg/min) diluted in 20 mL of 0.9% NaCl solution, at 20-min intervals. Heart rate and hemodynamic data were recorded just after the end of each AVP dose (or placebo) infusion in both groups.

Statistical analysis was performed by applying Student’s t-test for unplanned observations or analysis of variance (ANOVA) for repeated-measures, followed by Dunnnett’s multiple comparison test. A value of p < 0.05 was considered significant. All statistical calculations were carried out using Sygma Stat for Windows (Jandel Scientific, CA, USA).

Results

The results are expressed as mean ± SEM. No statistically significant alterations in the hemodynamic parameters were observed during vasopressin infusion at the lowest dose (0.01 U/kg/min) compared to the CONTROL group or to the baseline values (p = NS).

At the intermediate dose (0.1 U/kg/min), vasopressin induced significant decreases in cardiac index (CI) and heart rate (HR), when compared to both CONTROL group and baseline values. Additionally, increases in MAP and SVRI were verified at the end of the 10-minute drug infusion period (p < 0.05) (Figure 1).

After the infusion of the highest vasopressin dose (1.0 U/kg/min), the previous changes observed in CI, HR (decrease) and in MAP and SVRI (increase) were exacerbated (p < 0.05) (Figure 1). Additionally, at this dose, the calculated pulmonary vascular resistance index showed a statistically significant increase (p < 0.05), mainly due to the greater decrease in CI, rather than a significant increase in MPAP (Figure 2).

Discussion

This study showed that the continuous infusion of vasopressin for 10 minutes at a “low dose” (0.001 U/kg/min) had no appreciable effects on HR, MAP, MPAP and CI in healthy anesthetized dogs. However, at “moderate” (0.1 U/kg/min) and “high” doses (1.0 U/kg/min), it increased MAP, SVRI and the PVRI. These doses also significantly decreased CI (or placebo) infusion in both groups.

The pressor effect of vasopressin is due to its action on the V1-receptors in vascular smooth muscle, and it is more predominant in the peripheral systemic arteriolar vasculature than in venous or pulmonary circulation. Additionally, vasopressin leads to the potentiation of catecholamine action on vascular smooth
muscle. Vasopressin also inhibits nitric oxide production in the vascular smooth muscle and acts on K<sub>ATP</sub> channels. Both of these actions lead to vasoconstriction, which, in conjunction with the effect on V<sub>1</sub>-receptors, result in MAP increase.

In 1895 Oliver & Schaefer first reported the effects of the posterior pituitary extract on blood pressure, and more recently it has been broadly used in situations that need MAP increase, such as in septic shock and cardiopulmonary resuscitation (CPR).

The use of vasopressin as an adjunct drug for catecholamine-dependent or refractory vasodilatory shock has been suggested, as there is an inappropriate autonomic response and an excessive inflammatory vasodilation in this condition. However, its ideal doses, as well as its safety during short and long-term use in this condition remain a matter of controversy.

The recommended doses of vasopressin to use in shock cases are relatively very low (0.01-0.04 U/min, or 0.00014-0.0006 U/kg/min), and aim at elevating the arterial pressure, as well as reducing the need for high doses of catecholamines. These recommended therapeutic doses are almost 20 to 100 times lower than the lowest dose (0.01 U/kg/min) we used in our experimental trial, which has shown no appreciable effects on hemodynamic parameters in healthy anesthetized animals, when compared to baseline values and to the control (placebo) group. These findings can be explained by the...
Effects of vasopressin on cardiovascular function

Figure 2 - A) Mean Pulmonary Artery Pressure (MPAP), B) Pulmonary Capillary Pressure (PCP) and C) Pulmonary Vascular Resistance Index (PVRI) in basal (bas), after saline (sal) and after injection, as continuous infusion, of 20 ml of NaCl 0.9% for three times in the control group (□); and after injection, as continuous infusion, of 0.01 U/kg/min, 0.1 U/kg/min and 1.0 U/kg/min doses in log10 of -2, -1 and 0 in the vasopressin group (■). The results are expressed as mean ± SEM. *p <0.05 vs. basal. #p <0.05 vs. control group.

fact that these dogs have a normal operating baroreceptor reflex system, which blunts the hemodynamic effect of low vasopressin doses\(^{31}\), or even of high doses\(^{32}\).

Otherwise, in baroreceptor-denervated dogs, as shown by Cowley et al\(^{31}\), the dose-response (blood pressure) curve for vasopressin is displaced to the left by a factor of 60-100 when compared to the curve for intact dogs, in whom the baroreceptor reflex was allowed to compensate. Additionally, in decapitated animals, this factor of displacement for vasopressin was 8,000 for doses that caused a 50-mmHg rise in systemic arterial pressure\(^{31}\). Consistent with these experimental findings is the observation that the dose-response curves for vasopressin in patients with idiopathic orthostatic hypotension (Shy-Drager’s syndrome) were markedly displaced to the left when compared to those of normal subjects\(^{34,35}\). Similar findings have also been reported in brain-dead patients\(^{36}\). Therefore, in patients with severe sepsis septic shock, an abnormal baroreceptor reflex system function, due to critical illness polynuropathy or to excessive inflammatory response, has been postulated as a possible mechanism for their high sensitivity to low-dose vasopressin in increasing blood pressure\(^{31}\).

The observed MAP increase, caused by vasopressin use, reinforces its use in vasodilatory shock. However, a SVRI increase may lead to decreased tissue perfusion and severe adverse events in patients needing high doses of continuous vasopressin infusion\(^{37}\). Indeed, in a recent publication, Westphal et al\(^{38}\), studying the effects of vasopressin on healthy and septic sheep, reported a reduction in the CI and an increase in the SVRI and PVRI, suggesting that these collateral effects may limit the use of this drug as the only vasopressor during septic shock. However, the simultaneous use of AVP and norepinephrine, considering their combined beneficial effects and reduced adverse events, could represent a useful therapeutic option in septic patients\(^{38}\).

In our study, “high-dose” vasopressin (1.0 U/kg/min) led to a significant increase in PVRI, but this was mainly due to the decrease in the CI and no significant increase was observed in the mean pulmonary artery pressure (MPAP) or in the pulmonary wedge pressure (PWP), as shown in Figure 2. Leather et al\(^{39}\), studying the effect of vasopressin on the right ventricle function in a dog model of experimental pulmonary hypertension, concluded that vasopressin causes pulmonary vasoconstriction and an important negative inotropic effect in the right ventricle, suggesting that vasopressin should be used cautiously when the right ventricle function is compromised.

Study limitations

The present study has some limitations. Firstly, we have measured only global hemodynamic parameters, and no regional or metabolic effects of vasopressin infusion were evaluated. Secondly, we used vasopressin doses that were ten to one thousand times higher than those routinely used in clinical practice for the management of vasodilatory shock. Thirdly, the time of vasopressin infusion was very short, and probably not long enough to elicit the full activation of the normal cardiovascular compensation mechanisms. And, finally, healthy animals were studied, and obviously the obtained data cannot be directly extrapolated to those expected to occur in septic human patients.

Conclusion

Continuous intravenous vasopressin infusion at logarithmically increasing doses (0.01; 0.1; and 1.0 U/kg/min) progressively induced significant increases in MAP and SVRI, with important negative inotropic and chronotropic cardiovascular effects on healthy anesthetized dogs.
Although these doses are ten to one thousand times higher than those routinely used for the management of human vasodilatory shock, our data confirm that vasopressin should be used carefully and under strict hemodynamic (and metabolic) monitoring in clinical practice, especially if doses higher than 0.01 U/kg/min are needed.

Potential Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Sources of Funding
This study was funded by FAPESP.

Study Association
This article is part of the thesis of master submitted by Luiz Cláudio Martins, from Universidade Estadual de Campinas.

References


