

# Vasopressin ~ new indications for an old drug

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## Abstract

Vasopressin is a hormone from posterior pituitary. It is an octapeptide referred often as arginine vasopressin and antidiuretic hormone. It is emerging as an important advance in the treatment of variety of shock states. The current interest is for the use of ventricular fibrillation, sepsis and cardio pulmonary bypass. The pressor actions are complex and not un-

derstood completely. It has unique action in reversing some of the pathophysiological vasodilatation processes that occur in advanced shock, which are refractory to catecholamine vasopressors. Vasopressin 40 IU in refractory ventricular fibrillation is noted as level 2B evidence. Though well-known drug for many years, it has found many new indications.

**Keywords:** Posterior pituitary, Vasopressin, Ventricular Fibrillation, Cardiopulmonary Bypass, Sepsis.

## Introduction

Posterior pituitary hormones are formed in the hypothalamic nucleus. Packets of material migrate as granules down axons to posterior lobe of pituitary where they are stored. The mechanism of release is not established but probably neurogenic.

Oxytocin is an octapeptide containing isoleucine and leucine whereas pressor principle is an octapeptide containing phenylalanine and arginine. This is referred as arginine vasopressin also known as antidiuretic hormone (ADH). It increases reabsorption of water in distal convoluted tubules of kidney. It has direct smooth muscle stimulant effect on blood vessels, including coronary and perhaps the cerebral vessels.

Vasopressin is emerging as an important advance in the treatment of variety of shock states. This has mainly arisen from increased understanding of its importance in the endocrine response to shock. There is current interest in use of vasopressin in treatment of shock due to ventricular fibrillation, hypovolemia, sepsis and cardiopulmonary bypass (CPB).

## Physiology of vasopressin in shock

It is released from posterior pituitary in response to increased serum osmolarity or reduced plasma volume. Major physiological role of vasopressin is regulation of water balance in normal conditions. It does not appear to play a major role in vascular regulation of blood pressure. High level of vasopressin in syndrome of inappropriate antidiuretic hormone (SIADH) secretion does not produce hypertension. The normal levels are <4pgm/ml. In shock state the levels of vasopressin rise via activation of aortic or carotid baroreceptors. The vasopressin levels are high up to 469pg/ml after cardiac arrest. High levels are noted in response to surgery, CPB, epidural and general anaesthesia, myocardial infarction, etc. However, it has been noted that prolonged hypovolemia, sepsis and CPB may lead to low levels too, which in turn can lead to severe vasodilation that may occur in advanced shock. The exact mechanism of its deficiency is not well understood but it is said to be due to exhaustion of secreting stores from neurohypophysis and hypothalamus after a prolonged stimulation of vasopressin release. Impaired autonomic function may depress the baroreceptor reflex mediated release. Both these occur in septic shock and after prolonged CPB.

## Mechanism of action

Pressor actions are complex and not understood completely. Acts via splanchnic renal (V2) and vascular (V1)

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receptors. They are not as well categorized as adrenergic receptors. It produces vasoconstriction in non-vital circulation via V1 by increasing intracellular calcium. How vasopressin causes vasoconstriction in some vascular beds and dilatation in others is unclear. However, endothelial nitric oxide (NO) plays a role. Vasopressin produces vasodilation in renal, pulmonary, mesenteric and cerebral vascular beds. Vasoconstriction occurs in skin, skeletal muscles, small bowel, and fat. It has similar action like the catecholamines. It also has unique action in reversing some of the pathological vasodilating processes that occur in advanced shock which are refractory to the catecholamine vasopressors. It inhibits ATP sensitive potassium channels in vascular smooth muscle. These in turn produce cellular hyperpolarization, which inhibits calcium channels. Intracellular calcium levels fall resulting in vasodilation. Secondly it inhibits inflammatory cytokines released in response to trauma and sepsis. This stimulates vascular endothelial production of NO leading to vasodilation.

Top summarize the exogenously administered vasopressin restores vasoconstriction mechanism and also inhibits pathological vasodilation responses.

Hemorrhage stimulates cortisol release, which is augmented by vasopressin release in addition to ACTH stimulation. It is released when 10% reduction in circulating blood volume occurs. The result is production of concentrated urine formed by a vasopressin concentration of as low as 5pg/ml. It also increases smooth muscle contraction, which leads to increased arterial pressure. Catecholamines of vasopressin secretions are higher in hemorrhagic shock than in any other type of shock state except possibly cardiac arrest or in those with acute pheochromocytomas.

## **Vasopressin and variceal hemorrhage**

Endogenous peptide acts directly on mesenteric vascular smooth muscle, increases vascular resistance, decreasing splanchnic blood flow and ultimately decreasing splanchnic blood flow and pressure. It has not shown conclusive evidence in placebo control trials on survival. Major complications include myocardial ischaemia, gastrointestinal symptoms of diarrhoea, abdominal cramps. Nitroglycerine was used to reduce cardiac complications. Synthetic somatostatin reduces splanchnic blood flow by vasoconstriction, reduces portal pressure and flow and has less effect on systemic circulation used in medical management of variceal bleed.

## **Vasopressin – Elderly**

Release large quantities of ADH in response to hypertonic saline load. Water retention is still less efficient in comparison to the young due to reduced end-organ response to this hormone. Diminished thirst, poor diet, use of diuretics predispose elderly patients to intravascular and intracellular dehydration.

## **Vasopressin – Brain death**

Brain death is accompanied by marked physiological instability and treatment is often necessary to maintain viability of donor organs. Hypotension results from loss of descending vasomotor control and is exacerbated by hemorrhage, massive diuresis for diabetes insipidus, dehydration therapy. Treatment consists of restoration of intravascular volume and vasopressin 0.5-1.5±g/hr.

## **Vasopressin and septic shock (VASST)**

Septic shock has mortality of 50-70%. In randomized clinical trial of low dose of vasopressin in medical/surgical patients with septic shock requiring >5±/ml or norepinephrine for >3hours, 19 patients received steroids. Patients who had severe septic shock in VASST study are ventilated, required high dose norepinephrine, frequently had bacteremia, and had important organ dysfunction within 24 hours. Steroids did not make any difference in the above factors. Landry et al administered low dose exogenous vasopressin 0.04 units/min to 10 patients in septic shock. The mean pressure, systemic vascular resistance (SVR) and vasopressin levels increased within 15 minutes after administration [1]. Several studies replicated these results.

In two randomized clinical trials conducted recently, where adrenergic vasopressors were unable to maintain mean arterial blood pressure in patients with vasodilatory shock, continuous infusion of vasopressin administered as life saving drug (0.04 to 0.1 units/min) stabilized cardio circulatory parameters, avoided renal, mesenteric, pulmonary and cardiac ischaemia and even ensured weaning from catecholamines [2].

The possible mechanisms of action are as follows [3]

1. Vasopressin administration results in increased perfusion of adrenal medulla [4]
2. Vasopressin is a possible stimulator for ACTH release resulting in increased plasma cortisol levels<sup>5</sup>
3. Vasopressin maintains fibrillation frequency and amplitude above threshold necessary for successful defibrillation [6]

4. Repeated administration of vasopressin maintains coronary perfusion pressure above threshold (20-30 mmHg) that is needed for successful defibrillation [7]
5. Vasopressin maintains vital perfusion by maintaining blood pressure even during severe metabolic insults [8]. It produces selective vasoconstriction of resistance vessels in non vital tissues while preserving perfusion in vital organs [9].

### Vasopressin in sudden cardiac arrest

Four published clinical trials are available in literature comparing vasopressin with epinephrine in cardiac arrest [10-12]. It has been found to be useful in intravenous dose of 40IU in refractory cardiac arrest. Administration after about 40 minutes of ACLS improved coronary perfusion pressures despite no improvement in survival. In 40 patients of refractory cardiac arrest vasopressin resulted in successful resuscitation and increase in 24-hour survival as compared to epinephrine. The new guidelines of American Heart Association (AHA) and European Resuscitation Council (ERC) records for CPR of adults with refractory ventricular fibrillation, 40 units of AVP or 1mg of epinephrine (class 2B) recorded as alternative intervention [13-15]. ERC, which is a major contributor for the International Liaison Committee on Resuscitation, has not included vasopressin in the algorithm and stated that further evidence is required before this agent is firmly recommended. Patients with asystole or pulseless electrical activity should be treated with epinephrine only.

### Drug interactions

Vasopressin is destroyed by gastric trypsin, it should be given intravenously. Has elimination half-life of 10-35 minutes. The antidiuretic effect is increased by concomitant administration of carbamazepine, chlorpropamide, tricyclic antidepressants, etc. The antidiuretic effect may be decreased by concomitant use of lithium, norepinephrine, heparin, etc.

### Complications

Hypotension, bradycardia, arrhythmias and MI have been reported. Venous thrombosis tremor, hyponatremia, urticaria, abdominal cramps, vomiting, bronchoconstriction have been reported. Ischaemic skin and mucous membrane lesions are also a known complication. Should be used with caution in patients with chronic nephritis, CHF, nitrogen retention, asthma, epilepsy and migraine [10,16].

### Dosing and drug availability

Vasopressin is available as 20units/ml injection to be diluted with 5% dextrose or normal saline for concentration of 0.1 to 1 unit/ml. It should be administered via a central vein. For vasodilatory shock in adults 0.01 to 0.1 units/min and paediatric practice 0.0003 to 0.002 units/kg/min or 0.01 should be titrated for best mean pressures, tapered over 2 to 4 hours.

### Summary

Vasopressin appears to be an effective tool in the management of vasodilatory shock associated with sepsis or cardiopulmonary bypass in adults. It has become a useful adjunct to vasopressor therapy in critically ill children with catecholamine-resistant hypotension (level 2B evidence) as an alternative to adrenaline in adult refractory CPR, and useful in hemorrhage due to variceal. Over the last decade it has emerged as a useful drug in refractory shock. Additional research is required to develop optimal dose titration and identify any age-related adverse effects.

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