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Low-dose Vasopressin Infusions for Vasodilatory Shock

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The use of low-dose vasopressin infusions has become an accepted alternative for the management of vasodilatory shock refractory to catecholamines. While a growing number of publications describe the use of vasopressin in adults, there are only a small number of reports of its use in children. This issue of *Pediatric Pharmacotherapy* will review the available studies supporting the use of vasopressin infusions in pediatric patients and provide information on administration and monitoring.

Mechanism of Action

Vasopressin is an endogenous hormone produced in the parvocellular and magnocellular neurons within the supraoptic and paraventricular nuclei of the hypothalamus. It is stored and released by the posterior pituitary gland in response to increases in plasma osmolality or as a baroreflex response to decreases in blood pressure and/or blood volume.

Vasopressin acts on at least four different receptor sites, all of which appear to contribute to its effects in shock. The vasoconstrictive effects of vasopressin are mediated through vascular V_1 receptors. Activity at these receptors produces activation of phospholipase C and blocks K^+-sensitive adenosine triphosphate channels allowing release of intracellular calcium into vascular smooth muscle and counteracting the effects of nitric oxide or atrial natriuretic peptide. The resulting vasoconstriction occurs predominately in the small vessels of the skin, skeletal muscle, small intestine, and fat.

Blood flow within the coronaries, as well as the cerebral, pulmonary, and renal vascular beds, is preserved, promoting shunting to those areas. This regional vasodilation is likely the result of a complex interplay of vasopressin activity at V_1 and endothelial V_3 and oxytocin receptor sites producing an increase in nitric oxide release.

The antidiuretic effects of vasopressin are mediated through V_2 receptors, which are coupled to adenylyl cyclase and generate increases in cyclic adenosine monophosphatase (cAMP). As a result of this activity, capillary permeability in the distal tubules and collecting ducts is altered, producing increased reabsorption of water and augmenting systemic blood volume.

In addition to these direct effects, vasopressin may also enhance or restore catecholamine sensitivity. Synthetic vasopressin (8-arginine vasopressin) acts at the same receptor sites as endogenous vasopressin, producing an identical physiologic response.[1-4]

Vasopressin in Shock

During shock, circulating vasopressin levels initially increase in an effort to maintain cardiovascular homeostasis, reaching values as high as 1,000 pg/ml. After this initial increase, however, plasma vasopressin levels appear to rapidly decline despite continued stress.[5,6] In a 1997 study of 19 adults with septic shock, Landry and colleagues from Columbia University found an average plasma vasopressin level at 6 hours of 3.1 ± 1.0 pg/ml, within the normal range (< 4 pg/ml) despite continued hypotension.[5]

In an observational study of 62 adults in septic shock, Sharshar and colleagues found that after an initial increase in vasopressin, one-third of their patients exhibited a relative vasopressin deficiency. Vasopressin levels in these patients were at or below normal, despite the presence of a systolic blood pressure below 100 mm Hg or hypernatremia.[7] A similar decline in vasopressin levels has been demonstrated in prolonged hemorrhagic shock. It has been speculated that this relative vasopressin deficiency during the later stages of shock may be the result of an impairment in baroreflex-mediated hormone secretion, possibly stemming from depletion of pituitary vasopressin stores.[5,7]

Use in Adults

As a part of their 1997 study, Landry and colleagues administered low-dose exogenous vasopressin (0.04 units/min) to 10 patients in septic shock.[5] Although this dose would not be expected to produce an elevation in blood pressure among normotensive patients; in these patients, mean systolic blood pressure increased from 92 to 146 mm Hg within 15 minutes. Systemic vascular resistance increased from 644 to 1,187 dynes• sec/cm^5. Serum vasopressin concentrations increased to an average of 100 pg/ml. Stopping the infusion resulted in a rapid fall in blood pressure. Restarting at a lower dose (0.01 units/min) in six patients produced an increase in serum vasopressin concentrations to 30 pg/ml and an increase in systolic blood pressure from 83 to 115 mm Hg.

Several subsequent studies have replicated these early results. In 1999, Malay, working as part of the Columbia University group, conducted a randomized, double-blind, placebo-controlled trial of low-dose vasopressin (0.04 units/min) in 10 adults with septic shock.[8] All patients were receiving catecholamines. At one hour, vasopressin produced an increase in systemic vascular resistance from 878±218 to 1,190±214 dynes•sec/cm^5 and in systolic blood pressure from 98±5 to 125±8 mm Hg. Values were unchanged in the placebo group. All five of the vasopressin-treated patients survived for the 24-hour study period, while two patients in the placebo group died of refractory hypotension. Based on the results of these studies, the authors concluded that vasopressin was a useful agent in the treatment of refractory septic shock.

In 2001, Tsuneyoshi and colleagues conducted a prospective case-controlled trial of vasopressin in 16 adults with vasodilatory septic shock.[9] All patients received vasopressin at a rate of 0.04 units/min for 16 hours. Systolic arterial pressure increased from 69.3±12.1 at baseline to 96.9±22.0 mm Hg two hours after the initiation of therapy. Systemic vascular resistance increased from 1,132±469 to 1,482±486 dynes•sec/cm^5•m^2. In the first nine patients, attempts to discontinue vasopressin at 16 hours led to a rapid decline in blood pressure over the first 30 minutes. In the remaining patients, vasopressin was continued as needed, with an average duration of infusion of 93±75 hours. The authors noted no adverse cardiac effects associated with the use of vasopressin and no effect on blood glucose or electrolytes. Serum lactate concentrations declined, and urine output increased during therapy, likely as a result of increased renal perfusion. Fifty-six percent of the patients survived to discharge.

Vasopressin infusions have also been studied in other hypotensive states, including postcardiotomy vasodilatory shock.[10-15] In 1997, Argenziano and coworkers conducted a prospective, randomized, placebo-controlled trial of vasopressin in 10 adults with vasodilatory shock.[10] All of the patients had required placement of a left ventricular assist device. Vasopressin, at a rate of 0.1 units/min, increased mean arterial pressure from 57±4 to 84±2 mm Hg and systemic vascular resistance from 813±113 to 1,188±87 dynes•sec/cm^5. Patients in the placebo group experienced no change in hemodynamics and required higher norepinephrine doses.

In 2002, Masetti and colleagues conducted an open-label study of vasopressin in 16 adults with hypotension following cardiopulmonary bypass.[13] All had failed to respond to maximal norepinephrine doses (> 30 mcg/kg/min). Vasopressin was administered at rates of 0.1 to 1 unit/min for an average of 58.8±37.3 hours. Systolic blood pressure increased from 89.6±7.9 to 119.6±10.5 mm Hg with treatment, and systemic vascular resistance increased from 688.0±261.7 to 1,043.3±337.1 dynes•sec/cm^5. Vasopressin use permitted discontinuation of other vasopressors in 13 of the patients, within an average of 5.8±7.8 hours. Seven of the 16 patients survived to discharge.

Use in Children

After their initial success with vasopressin in adults, the Columbia University investigators extended their research to pediatric patients. In 1999, Rosenzweig and colleagues reported the results of using vasopressin in 11 children (ages 3 days to 15 years, median 35 days) with vasodilatory shock after cardiac surgery.[16] All patients had profound hypotension unresponsive to catecholamine therapy. Plasma vasopressin levels measured in three patients prior to therapy were low, with a median of 4.4 pg/ml.

Exogenous vasopressin was administered with a weight-adjusted dose ranging from 0.0003 to 0.002 units/kg/min (equivalent to 0.3 to 2 milliunits/kg/min). The mean duration of therapy was 71±46 hours (range 6 to 144 hours). Vasopressin was initiated in five patients immediately after cardiopulmonary bypass, in another five within 12 hours of surgery, and in one child on the second postoperative day. Systolic blood pressure rose within the first hour of administration from 65±14 to 87±17 mm Hg. The use of other inotropes declined significantly in nine patients and was unchanged in the other two. Urine output, electrolytes, and perfusion remained unchanged. Nine children survived.

The following year, Katz and coworkers published a retrospective review of vasopressin use in 34 children undergoing brain death evaluation and/or awaiting organ donation.[17] The patients were given vasopressin as a part of a routine protocol to treat diabetes insipidus, with dose titration based on urine output. The vasopressin dose varied considerably among the patients, with a mean of 0.041±0.069 units/kg/hr (equivalent to 0.68±1.15 milliunits/kg/min). Compared to a group of 29 age-matched controls, the children who were given vasopressin had significantly higher mean arterial pressures (80±14 versus 68±22 mm Hg for controls) at the time of organ recovery and required less vasopressor support. There were no adverse effects attributed to vasopressin.

In 2002, O'Blenes and colleagues described a case of severe phenoxybenzamine-induced hypotension that responded to vasopressin.[18] Phenoxybenzamine had been administered to improve systemic oxygen delivery following cardiac surgery in an 8 day old infant with hypoplastic left heart syndrome. After 17 hours of phenoxybenzamine administration, the patient developed profound hypotension with anuria. When norepinephrine failed to improve blood pressure, vasopressin was initiated. The dose was titrated from 0.3 to 0.6 milliunits/kg/min. Blood pressure and urine output improved, allowing reduction and subsequent discontinuation of the norepinephrine. Vasopressin was continued for 37 hours. The patient was discharged on postoperative day 16.

Pharmacokinetics

Because vasopressin is destroyed by gastric trypsin, it must be administered parenterally. Vasopressin is rapidly degraded by enzymes in the liver and kidneys, with an elimination half-life of approximately 10 to 35 minutes.[1-4,19]

Drug Interactions

The vasoconstrictive effects of vasopressin are counteracted by vasodilators such as nitroglycerin or nitroprusside. The antidiuretic effect of vasopressin is increased by concomitant administration of carbamazepine, chlorpropamide, clofibrate, fludrocortisone, tricyclic antidepressants, or urea. The antidiuretic effect of vasopressin may be reduced by concurrent use of demeclocycline, heparin, lithium, or norepinephrine.

Adverse Effects

High dose vasopressin administration has been associated with hypertension, bradycardia, arrhythmias, and myocardial infarction. These adverse effects have been reported most frequently in patients with cardiovascular disease. Administration of vasopressin without adequate fluid resuscitation may also result in significant ischemia of other organs, including the gastrointestinal tract and kidneys.

The development of ischemic skin and mucous membrane lesions is a known complication of vasopressin therapy, resulting from the intense vasoconstriction produced within the capillaries.[20] Ischemic lesions have been estimated to occur in as many as 10 to 30% of patients receiving low-dose vasopressin infusions. Extravasation of vasopressin from an infusion site can also produce intense local vasoconstriction, which may result in severe tissue necrosis and gangrene. The skin, particularly around the site of infusion, should be closely inspected on a regular basis to identify any signs of decreased perfusion.

Other adverse effects associated with vasopressin include: venous thrombosis, tremor, vertigo, sweating, hyponatremia, urticaria, abdominal cramps, vomiting, and bronchial constriction. Hypersensitivity reactions, including anaphylaxis, have also been reported. Because of the ability of vasopressin to rapidly increase extracellular water content, it should be used with caution in patients with chronic nephritis and nitrogen retention, congestive heart failure, asthma, epilepsy, or migraines.[3,4]

Dosing and Drug Availability

Vasopressin is available as a 20 unit/ml injection. For continuous intravenous infusion, it should be diluted with normal saline or 5% dextrose to a final concentration of 0.1 to 1 unit/ml. Administration through central venous access is recommended to minimize the risk of extravasation. Although the stability of vasopressin infusions with other drugs has not been studied, a recent report on bolus vasopressin administration found it to be compatible with amiodarone, diltiazem, dobutamine, dopamine, epinephrine, heparin, lidocaine, milrinone, nitroglycerin, norepinephrine, phenylephrine, and procainamide.[21]

Studies of vasopressin in adults with vasodilatory shock have used infusion rates of 0.01 to 0.1 units/min.[10-15] In an abstract presented at the 2003 Critical Care Congress, a retrospective review of high versus conventional vasopressin doses showed no additional benefit from doses greater than 0.08 units/min.[22] In pediatric patients, a vasopressin dose of 0.3 to 2 milliunits/kg/min (equivalent to 0.0003 to 0.002 units/kg/min or 0.01 to 0.12 units/kg/hr) is

recommended, based on the report by Rosenzweig.[16] The infusion should be titrated to optimize blood pressure and perfusion. It has been suggested that vasopressin infusions may be tapered over a 2 to 3 hour period, once blood pressure and the doses of concomitant catecholamine infusions are stabilized.[14]

Summary

Vasopressin appears to be an effective tool in the management of vasodilatory shock associated with sepsis or cardiopulmonary bypass in adults. Although only a few papers describe its use in pediatric patients, it may become a useful adjunct to traditional vasopressor therapy in critically ill children with catecholamine-resistant hypotension. Additional research is needed to develop an optimal range for dose titration and identify any age-related adverse effects.

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Pharmacology Literature Review

Pravastatin in Children

The pharmacokinetics and pharmacodynamics of pravastatin, an HMGCo-A reductase inhibitor, were evaluated in 20 children (ages 4-15 years) with familial hypercholesterolemia. Patients received a 10 mg oral dose daily for 8 weeks. The mean peak plasma concentration was 15.7 ng/ml, and the half-life was 1.6 hours, similar to values in adults. Total cholesterol decreased 18%, with a decrease in low-density lipoprotein cholesterol of 21%. None of the patients had elevation of liver function tests or creatinine. Hedman M, Neuvonen PJ, Neuvonen M, et al. Pharmacokinetics and pharmacodynamics of pravastatin in children with familial hypercholesterolemia. **Clin Pharmacol Ther 2003;74:178-85.**

Formulary Update

There was no meeting of the Pharmacy and Therapeutics Committee in August.

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