Vasopressin: A Review of Therapeutic Applications
Natalie F. Holt, MD, MPH,*† and Kenneth L. Haspel, MD*†

Vasopressin (VP) was discovered in 1895 from the extract of the posterior pituitary and named for the early observation of its vasoconstrictive properties.¹ The peptide is present in various species, both invertebrate and vertebrate, with only minor variations in amino acid sequence. Human VP contains the amino acid arginine, hence the name arginine vasopressin. It is alternatively referred to as antidiuretic hormone (ADH), reflecting its main physiologic function in promoting water retention. (For the remainder of the text, the term vasopressin and the abbreviation VP will be used in lieu of arginine vasopressin or antidiuretic hormone.)

Since its isolation² and synthetic preparation,³ VP has been the subject of much research. Its clinical applications range from the management of enuresis to the treatment of gastrointestinal hemorrhage, septic shock, cardiac arrest, and heart failure. The purpose of this review is to provide an overview of the physiology and pharmacology of this hormone and its various functions. As with much in medicine, the discovery of disease states involving VP and/or its receptors has offered the most insight into VP’s in vivo role and functional repertoire. As such, an appraisal of these conditions will be used to review current knowledge and clinical applications of VP and its synthetic agonists and antagonists. Unanswered questions and future research opportunities will then be summarized.

Vasopressin Physiology and Pharmacology

Vasopressin Synthesis and Regulation

VP contains 9 amino acids, including 2 cysteines bridged by a disulphide bond. The gene for VP is on chromosome 2 and neighbors that of oxytocin. The 2 hormones are structural cousins, differing only by 2 amino acids.⁴,⁵ VP is synthesized in the magnocellular and parvocellular neurons of the hypothalamic paraventricular and supraoptic nuclei (Fig 1). It is transcribed as a larger prohormone with the carrier protein neurophysin, and it is cleaved into its final form while in transit via the supraoptic-hypophyseal tract to secretory granules in the posterior pituitary gland.⁶ Upon stimulation, VP is released from its storage granules and rapidly enters the bloodstream via the well-vascularized posterior pituitary capillary bed, which is devoid of a blood-brain barrier.

The most important stimulus for VP release is a change in plasma osmolality that is sensed via peripheral receptors near the portal vein and central receptors near the third ventricle. Information from peripheral receptors ascends via the vagus nerve through the medulla to the hypothalamic nuclei. The system is precisely regulated to maintain plasma osmolality between 285 and 295 mOsm/kg H₂O. There is a linear relationship between plasma VP concentrations and plasma osmolality, and a change on the order of only 1 pg/mL in VP concentration produces a measurable adjustment in urine specific gravity.⁶

VP is also responsive to changes in blood pressure, as sensed by baroreceptors in the left heart, aortic arch, and carotid sinus. Under ordinary physiologic conditions, VP has a limited role in blood pressure regulation. Evidence for this is in the lack of hypertensive effect seen among patients with the syndrome of inappropriate antidiuretic hormone secretion (SIADH), in which concentrations of VP are well above normal levels.⁷ Whereas an alteration in plasma osmolality of only 1% effects a measurable change in plasma VP concentrations, blood pressure must drop by more than 10% to stimulate VP release.⁶ However, with significant drops in blood pressure, plasma VP concentrations increase exponentially, in contrast to the linear VP response seen with changes in osmolality.⁴

Other conditions have been noted to alter VP release either in vivo or in vitro; these include pain, hypoxemia, and hypoglycemia.⁸ Acetylcholine, histamine, catecholamines, prostaglandins, and nitric oxide (NO) appear to stimulate VP release, whereas opioids seem to inhibit VP release.⁹ Furthermore, a role for VP has been postulated in human functions other than osmo- and baroregulation, including social behavior¹⁰ and temperature regulation.¹¹

Normal plasma VP concentrations vary among individuals but are usually on the order of 1 to 5 pg/mL. Diurnal variation is observed, with a nighttime increase to approximately 2 times that of daytime levels.¹² The half-life of VP is between 5 and 20 minutes.¹³ It is metabolized in the liver and kidneys. VP release triggers a number of negative feedback loops. The reduction in plasma osmolality inhibits VP synthesis. Adrenocorticotropic hormone (ACTH), whose release is stimulated by VP, increases glucocorticoid concentration, which inhibits VP secretion. In addition, VP induces a structural change in its own receptors, which inhibits their downstream interaction with G-proteins.

From the *Veterans Affairs Connecticut Healthcare System, West Haven Campus, West Haven, CT; and †Department of Anesthesiology, Yale University School of Medicine, New Haven, CT.

Address reprint requests to Natalie F. Holt, MD, MPH, Veterans Affairs Connecticut Healthcare System, West Haven Campus, Department of Anesthesiology, 950 Campbell Avenue, West Haven, CT 06516. E-mail: natalie.holt@va.gov

Published by Elsevier Inc.
10.1053/j.jvca.2009.09.006

Key words: vasopressin, vaptans, arginine vasopressin, antidiuretic hormone, vasopressors

and results in cell sequestration of membrane-bound receptors. Approximately 10% to 20% of VP stores are available for immediate release in response to stimulation. Secretion diminishes with persistent stimulation, as suggested by the biphasic course of plasma VP concentrations in pathologic conditions such as septic shock. Orally administered VP is rapidly hydrolyzed by trypsin, rendering it inactive. Therefore, exogenous VP must be administered parenterally and by continuous infusion because of its short half-life.

**Vasopressin Receptor Distribution and Signaling Pathways**

**Receptor Subtypes and Distribution**

VP receptors are widely distributed in the body, and 3 distinct receptor subtypes have been identified (Table 1). V1 (also referred to as V1a) receptors are found primarily on vascular smooth muscle where they contribute to vasoconstriction, especially in vascular beds of the mesentery, skin, and...
skeletal tissues. They also are present on platelets where they promote platelet aggregation. In the liver, V1-receptor activation stimulates glycogenolysis and glucose secretion. In the adrenal gland, it promotes aldosterone and cortisol release. V1 receptors also have been found in the myometrium where they mediate uterine contractions. V1 receptors are selectively distributed in the kidney as well, such that activation constricts efferent but not afferent arterioles.\(^5\) This effect appears to be mediated by local release of NO\(^1\) and accounts for the observation that, although VP given to patients in shock states promotes vasoconstriction, it also tends to increase glomerular filtration rate and urinary output. Finally, there are V1 receptors in the central nervous system, including the hypothalamus, amygdala, and cerebellum. V1 receptors in the brainstem seem to enhance baroreceptor-mediated inhibition of sympathetic nervous system (SNS) activity;\(^19\,20\) they also are postulated to have a role in other complex functions such as social memory, stress adaptation, and mood.\(^21\)

Although V1 receptors are present in the kidney, V2 receptors predominate and are concentrated on cells of the distal convoluted tubule and collecting duct. V2-receptor activation in the kidney stimulates gene transcription and cell membrane integration of aquaporin channels on renal collecting duct cells. Water is then translocated to the basolateral cell surface and returned to the intravascular compartment. V2 receptors are also expressed on the vascular endothelium, as evidenced by the increased levels of von Willebrand factor (vWF), factor VIII, and plasminogen activator that accompany the administration of V2-receptor agonists.\(^5\,22\)

V3 (also called V1b) receptors have been identified in the anterior pituitary and elsewhere in the central nervous system. Through these receptors, VP is believed to act as a neuromodulator. It appears to stimulate ACTH secretion via the activation of the corticotropin-releasing hormone (CRH). This is supported by the observation that exogenously administered CRH with VP result in substantially higher plasma cortisol levels compared with the administration of CRH alone.\(^13\,21\) Furthermore, during cardiopulmonary resuscitation (CPR) and early sepsis, short-term rises in serum ACTH and cortisol levels have been observed in patients treated with VP compared with catecholamines.\(^24\,25\) V3-receptor activation also seems to promote the secretion of other hormones, including prolactin, growth hormone, insulin, angiotensin, endothelin, and atrial natriuretic peptide (ANP), although the in vivo relevance of these properties remains to be established.\(^26\)–\(^29\) Finally, V3 receptors have possible roles in social behavior and regulation of mood.\(^21\,30\,31\)

Consistent with the observed molecular similarity between VP and oxytocin, VP has been found to interact with oxytocin receptors, although with an affinity approximately one-tenth as great as that of oxytocin. Recently, the interaction of VP with cardiac oxytocin receptors has been found to promote ANP release and subsequent natriuresis.\(^32\) The role of this system in vivo has yet to be fully elucidated.

VP also has activity at purinergic receptors, whose intrinsic ligand is the phosphate moiety of adenosine triphosphate.\(^5\) In guinea pigs, VP infused into the coronary circulation has been found to cause vasoconstriction via interaction at purinoreceptors in the cardiac endothelium.\(^33\) However, these results have not been reproduced consistently in vitro\(^34\) or animal models,\(^35\) and the clinical significance of VP’s affinity for the purinoreceptor in humans remains to be shown.

### Downstream Signaling

VP activity is mediated intracellularly through second messengers (Fig 2). V1 and V3 receptors act via a phosphatidylinositol pathway, producing inositol triphosphate and diacylglycerol, which, in turn, activate protein kinase C and increase intracellular calcium entry. In contrast, V2 receptor effects are mediated by adenyl cyclase and cyclic adenosine monophosphate.\(^1\,2\,36\) As previously mentioned, other mechanisms for VP action, including locally induced NO release, also have been described.\(^18\)

### Table 1. Distribution and Function of VP Receptors

<table>
<thead>
<tr>
<th>VP Receptor Subtype</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1 Vascular smooth muscle</td>
<td>Platelets</td>
<td>Vasoconstriction (mesentery, skin, skeletal tissue)</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>Aldosterone and cortisol release</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>Glycogenolysis and glucose release</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Peristalsis</td>
<td></td>
</tr>
<tr>
<td>Myometrium</td>
<td>Uterine contraction</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>Regulation of blood pressure and heart rate</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>Role in emotional learning, social memory, circadian rhythm, stress adaptation</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>Free water resorption via gene transcription and cell membrane integration of aquaporin channels on renal collecting duct cells</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>Vasodilation</td>
<td></td>
</tr>
<tr>
<td>Kidney Anterior pituitary</td>
<td>Release of von Willebrand factor, factor VIII</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>Neurmodulation → corticotrophin, growth hormone, prolactin secretion</td>
<td></td>
</tr>
<tr>
<td>Kidney Brain</td>
<td>Stress adaptation</td>
<td></td>
</tr>
<tr>
<td>Kidney Pancreas</td>
<td>Insulin synthesis and release</td>
<td></td>
</tr>
<tr>
<td>Kidney Heart</td>
<td>Atrial natriuretic peptide synthesis and release</td>
<td></td>
</tr>
</tbody>
</table>

\(^*\) The in vivo relevance of these properties remains to be established.\(^26\)–\(^29\)
Synthetic Vasopressin Analogs

The development of VP analogs with longer half-lives and receptor-specificity greatly enhanced the practical application of VP therapy. In 1968, octapressin was shown to improve renal blood flow in patients with cirrhosis. In 1985, Lenz et al found similar effects with another synthetic analog, orni-pressin. At present, the only clinically used VP analogs are terlipressin (TP) and desmopressin (DDAVP) (Fig 3).

TP

TP (triglycyl lysine vasopressin) is a 12 amino acid peptide whose active metabolite is lysine vasopressin. Relative to VP, it exhibits a greater degree of V1-receptor specificity (2.2:1 compared with 1:1 for AVP). Because lysine vasopressin is released into the systemic circulation gradually, when compared with VP, TP has a longer duration of action that allows for bolus injection. However, because bolus dosing has been linked to a higher frequency of systemic side effects, including myocardial ischemia and skin necrosis, continuous infusion therapy is favored. Like VP, TP is only available for parental use. Of note, TP, but not VP, has been shown to dilate intrahepatic vessels, thereby enhancing blood flow through the hepatic artery in patients with cirrhotic liver disease and portal hypertension. TP has been available in Europe and Asia for more than 2 decades where it is considered the treatment of choice for the emergency management of bleeding esophageal varices. In addition, it is used “off-label” in treating patients with refractory arterial hypotension. In 2004, the United States Food and Drug Administration (FDA) granted TP orphan drug status as the only therapy being studied for the treatment of patients with acute and rapidly progressive hepatorenal syndrome (HRS); the following year, it was placed on the “fast track” for FDA New Drug Approval where it remains at the time of this publication.

DDAVP

DDAVP (1-deamino-8-D-arginine vasopressin) was the first and remains the only clinically available VP agonist with V2-receptor specificity (V2:V1 receptor affinity approximately 2,000-3,000 times that of VP). Intravenous, intranasal, subcutaneous, and oral preparations of DDAVP are now standard treatment for patients with central diabetes insipidus (DI). In the 1970s, 2 independent research groups discovered that DDAVP increased the release of vWF and factor VIII. This led to the use of prophylactic DDAVP to reduce perioperative bleeding in patients with some types of von Willebrand disease as well as hemophilia and uremia-induced platelet dysfunction (see section on Disorders of Hemostasis).

Vasopressin Antagonists

Hyponatremia is one of the most common diagnoses in hospitalized patients, occurring in the context of many conditions, including the syndrome of inappropriate antidiuretic hormone (SIADH) secretion, congestive heart failure, and cirrho-
sis. Although fluid restriction and diuretics are often effective at treating hyponatremia, prolonged treatment may impair renal function. In the 1990s, several nonpeptide vasopressin antagonists, also called vaptans, were developed to oppose VP-induced free water conservation present in these conditions. Conivaptan is a parenterally formulated vaptan and the only vaptan with substantial activity at both V1 and V2 receptors. Several other vaptans including tolvaptan, lixivaptan, moza-vaptan, and satavaptan are specific V2-receptor antagonists and are available in oral form. All have shown therapeutic efficacy in terms of increasing urine output and raising serum sodium concentrations. They are generally well tolerated, with thirst and dry mouth being among the most common side effects. Vaptans are hepatically metabolized; conivaptan is a potent inhibitor of the CYP34A enzyme, and, as such, its use can alter the serum concentrations of many concomitantly delivered drugs.

### VASOPRESSIN IN PATHOPHYSIOLOGIC CONDITIONS: DISORDERS OF PLASMA OSMOLALITY

**DI**

DI is a condition characterized by the excess production of inappropriately dilute urine. Loss of free water in excess of solute leads to plasma hyperosmolality. The following 2 main causes of DI are recognized: (1) a lack of VP secretion (pituitary or central DI) and 2) an impaired renal response to VP (nephrogenic DI). Central DI is acquired and may occur from a brain tumor, infection, injury, or status postpituitary surgery. DDAVP is now the mainstay of treatment for central DI. In addition, DDAVP is used in the temporary treatment of nocturnal enuresis, which is caused by a maturational delay in the normal nocturnal increase in VP secretion.

Nephrogenic DI may be acquired or congenital. Genetic defects in the V2 receptor, which is encoded on the X chromosome, are responsible for most cases of congenital nephrogenic DI. Defects in the aquaporin channel, encoded on chromosome 12, also can cause congenital nephrogenic DI. Certain drugs, most notably lithium, interfere with the kidney’s ability to respond to VP and are responsible for acquired cases of nephrogenic DI. Relative to congenital cases, acquired nephrogenic DI is usually of a milder form. Because patients with nephrogenic DI do not respond appropriately to VP, DDAVP is ineffective. To date, treatment has consisted of a low-sodium, low-protein diet; aggressive hydration; and the possible addition of nonsteroidal anti-inflammatory drugs and/or diuretics, which, paradoxically, reduce urinary output in these patients. Recent research indicates that V2-receptor antagonists may help stabilize mutant VP receptors responsible for some cases of nephrogenic DI and thereby improve their responsiveness to endogenous VP. However, investigations in this area are still preliminary, and clinical application remains unclear.

### Hyponatremia

**SIADH**

SIADH describes a condition in which there is dysregulation of VP secretion. The hallmark of SIADH is euvolemic hyponatremia and urine osmolality in excess of plasma osmolality. First described in the late 1950s, SIADH is one of the most common diagnoses in hospitalized patients. It is observed in...
vasopressin

conjunction with a number of pathologic states, including HIV infection and tumors that produce ectopic VP (eg, pulmonary small-cell carcinoma). SIADH is also a common postoperative condition in which pain may contribute to excess VP secretion. In addition, medications are known to cause SIADH, including phenothiazines, tricyclic antidepressants, nicotine, carbamazepine, and antineoplastic drugs such as vincristine and cyclophosphamide.

Most cases of SIADH are temporary and may be managed by fluid restriction and/or diuretic therapy. In more severe or chronic conditions, drug therapy may be required. Demeclocycline, a tetracycline agent, was traditionally a preferred pharmacotherapeutic option. Demeclocycline interferes with the cellular response to VP in the kidney by impairing the formation of the second messenger cyclic adenosine monophosphate. Lithium also interferes with the renal response to VP secretion, but side effects precluded its routine use as a treatment for SIADH.

The development of VP antagonists has introduced a new treatment option for patients with severe cases of SIADH and other chronic illnesses that cause symptomatic hyponatremia or fluid retention. Intravenous conivaptan is the only vaptan FDA-approved for the treatment of euvolemic or hypervolemic hyponatremia in hospitalized patients (Table 2). Treatment with conivaptan consistently increases urinary output and raises serum sodium concentrations. At doses used in clinical practice, there is no effect on systemic blood pressure, although at high doses hypotension may occur because of V1-receptor blockade.

**Congestive Heart Failure and Cirrhosis**

Hyponatremia has been found to be an independent predictor of major complications, rehospitalization, and mortality in patients with congestive heart failure. In a post hoc analysis of data from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness trial, baseline and persistent hyponatremia were found to be independent predictors of hospitalization for heart failure and mortality over a 6-month follow-up period. Among these patients, suppression of VP release that would be expected because of hyponatremia is overridden by baroreceptor activation in the aortic arch and carotid sinus resulting from low cardiac output. Enhanced activity of the renin-angiotensin-aldosterone system (RAAS) also may promote VP secretion.

Gheorghieade et al studied the impact of 3 doses of tolvaptan in a double-blind placebo-controlled trial of 254 patients with chronic heart failure. Over the 25-day study period, reductions in body weight and edema, as well as normalization of serum sodium concentration in hyponatremic patients, were observed in patients treated with tolvaptan but not placebo. Tolvaptan therapy was well tolerated and produced no appreciable changes in heart rate, systemic blood pressure, or renal function. Interestingly, only 6.3% of the study population had abnormal VP levels at baseline, and tolvaptan treatment did not produce a statistically significant increase in VP levels; therefore, tolvaptan’s therapeutic mechanism of action has yet to be fully established. However, the results of this trial have since been substantiated by several other large-scale, randomized, placebo-controlled studies, including the Acute and Chronic Therapeutic Impact of Vasopressin Antagonist in Congestive Heart Failure trial and the Efficacy of Vasopressin Antagonist in Heart Failure Study with Tolvaptan trial.

Other trials of V2 antagonists have been conducted among patients with hyponatremia from cirrhosis, SIADH, and congestive heart failure. All have shown efficacy in terms of normalization of serum sodium concentration. Many have reported symptomatic benefits including reduced edema and increased ease of breathing. One study identified improvements in self-assessed mental health over a 30-day treatment period. Whether serum sodium normalization confers benefit in terms of morbidity and mortality remains uncertain. In animal models of congestive heart failure, V1/V2 antagonist therapy has been shown to improve fluid regulation and reduce cardiac hypertrophy. Studies in humans have exhibited mixed results. A few short-term trials with conivaptan and tolvaptan have shown reductions in right atrial and pulmonary artery occlusion pressures and modestly improved left ventricular function. However, in a 12-week placebo-controlled trial of oral conivaptan therapy in patients with class III heart failure, no impact on functional capacity or exercise tolerance was shown.

The Multicenter Evaluation of Tolvaptan Effect On Remodeling trial studied the impact of long-term tolvaptan therapy in a group of 240 patients with New York Heart Association class II or III heart failure and ejection fractions <30%. In a 1-year follow-up, tolvaptan-treated patients exhibited statistically non-significant increases in left ventricular ejection fraction; in addition, there was a trend toward lower rates of mortality and heart failure–related hospitalizations. However, in the Efficacy of Vasopressin Antagonist in Heart Failure Study with Tolvaptan trial, the largest study to date, investigators were unable to identify improvement in heart function, physical health, or overall mortality over a median 9.9-month follow-up period. Patient recruitment is now underway for the BALANCE study, a phase III randomized multicenter double-blind, placebo-controlled, parallel study of oral lixivaptan for the management of hyponatremia in patients hospitalized for heart failure. BALANCE will study the safety and efficacy of oral lixivaptan for increasing serum sodium concentration and will assess the impact of therapy on rehospitalization as well as all-cause and cardiovascular mortality.

**DISORDERS OF HEMOSTASIS**

von Willebrand Disease and Disorders of Coagulation

In the 1970s, 2 research groups independently discovered that DDAVP enhanced the release of factor VIII, vWF, and plasminogen activator, thereby promoting platelet aggregation and coagulation. This effect is mediated via V2 receptors present on the vascular endothelium. Mannucci et al were the first to show the effectiveness of DDAVP in reducing bleeding during dental extraction in a group of 25 patients with hemophilia A or von Willebrand disease. Since then, DDAVP has achieved widespread use in the perioperative management of patients with von Willebrand disease type 1, which results from a partial quantitative reduction in vWF. DDAVP is tran-
siently effective in most patients with von Willebrand disease types 2A, 2M, and 2N, which are caused by qualitative vWF defects, although its prophylactic use in these patients is more controversial.\textsuperscript{51,52,108} Paradoxically, in patients with von Willebrand disease type 2B, DDAVP may cause thrombocytopenia and thereby increase bleeding risk.\textsuperscript{52} DDAVP is also used to reduce perioperative bleeding in patients with hemophilia A and other conditions associated with coagulation dysfunction, such as uremia\textsuperscript{109–111} and cirrhosis.\textsuperscript{112–115} In addition, it has proven effective at improving platelet function and reducing blood loss in patients treated with antiplatelet agents such as aspirin and ticlopidine.\textsuperscript{112,116–119} The mechanism of this effect appears to involve more than stimulation of procoagulant release but remains to be fully explained.\textsuperscript{120}

Perioperative Bleeding

In the 1980s, speculation was raised that prophylactic DDAVP administration might help reduce blood loss in patients without intrinsic bleeding disorders who were undergoing complex surgical procedures at risk for large blood loss. Initial favorable results were reported by several groups in the context of spinal fusion, major joint arthroplasty, and cardiac surgeries.\textsuperscript{118,120,121} However, subsequent studies and several meta-analyses failed to reproduce these benefits.\textsuperscript{92,122–129} In a meta-analysis of 12 randomized controlled trials of DDAVP in cardiac surgery, Cattaneo et al\textsuperscript{50} in fact found more than double the incidence of myocardial infarction in DDAVP-treated patients compared with placebo-treated controls (4.4% v 1.6%), although the result was not statistically significant. Therefore, although DDAVP may help promote surgical hemostasis, its use seems best reserved for select cases.\textsuperscript{50,92,127,130–132}

Variceal Bleeding

In patients with cirrhotic liver disease, fibrotic tissue impairs infrahepatic blood flow, leading to the formation of dilated splanchnic collateral vessels and portal venous hypertension. Because of their high pressure and large shunt volume, rupture of these collaterals is often a lethal complication of advanced liver disease. Both VP and TP are first-line therapies in the management of variceal hemorrhage because both have powerful vasoconstrictive effects in splanchnic vascular beds. Compared with VP, TP appears to have a wider safety profile and is also the only drug that has shown a survival benefit compared with placebo.\textsuperscript{133} However, TP remains unavailable in the United States.

DISORDERS OF HYPOPERFUSION

Hepatorenal Syndrome

Patients with portal hypertension and cirrhosis develop a state of relative arterial hypotension caused by distention of splanchnic blood vessels and underfilling of the central arterial tree. This results in activation of the RAAS and SNS, which promotes water and sodium retention and vasoconstriction. RAAS activation and relative central hypovolemia impair blood flow to vital organs. Progressive renal failure originating from liver cirrhosis is one of the most difficult complications to treat and as such is associated with a high level of morbidity and mortality. Two forms of HRS are recognized; type I HRS is rapidly progressive and usually results in death within days to weeks unless liver transplantation is performed. The course of type II HRS is more variable; however, median survival is on the order of 6 months.\textsuperscript{134}

In addition to splanchnic vasoconstriction, TP has been found to reduce portal venous pressure and blood flow through portosystemic shunts as well as to dilate infrahepatic blood vessels, leading to increased hepatic blood volume. To the extent that the latter effect restores blood volume to the central circulation, there is attenuation of RAAS and SNS-mediated vasoconstriction, which increases renal blood flow and helps preserve renal function. TP is now under active investigation in the management of patients with type I HRS as a bridge therapy to liver transplant. In clinical trials, treatment has been shown to improve both renal and cardiovascular function and possibly confer survival benefit.\textsuperscript{133,135–139} Current evidence supports early intervention to maximize treatment benefits.

Septic Shock

Septic shock represents a pathologic state in which vasodilation results in hypoperfusion and ultimately end-organ dysfunction. Absolute and relative hypovolemia are frequently present as a result of fever-induced evaporative and gastrointestinal losses and fluid extravasation from the intravascular space caused by capillary leak. In addition, pathologic vasodilation persists despite significant reductions in systemic blood pressure. Multiple mechanisms appear to mediate this response, including increased NO production and activation of potassium channels that relax vascular smooth muscle.\textsuperscript{140–142}

In the early phase of sepsis, VP levels are acutely elevated and then decline rapidly as the condition progresses.\textsuperscript{143–148} The depletion of endogenous VP appears to contribute to the vasodilation associated with advanced sepsis.\textsuperscript{149} and an inverse relationship between patient survival and endogenous serum VP levels in the late stage of shock has been observed.\textsuperscript{150} As a potent secretagogue, endotoxin may deplete glandular stores of VP.\textsuperscript{151–153} High levels of circulating catecholamines and NO also have been shown to suppress VP release.\textsuperscript{154} Impaired baroreceptor-mediated VP secretion seems also to play a role.\textsuperscript{140,146}

Landry et al\textsuperscript{146} were the first to report that the infusion of exogenous VP in a series of 5 patients with septic shock produced a measurable improvement in vascular tone and increased urinary output (Table 2).\textsuperscript{146} This is in contrast to the negligible hypertensive effect of exogenous VP when administered to healthy, euvolemic adults.\textsuperscript{146} The Vasopressin and Septic Shock Trial was a multicenter, randomized trial aimed at assessing the impact of adding VP to norepinephrine therapy in treating patients with septic shock.\textsuperscript{150} The study involved 779 patients. Adverse events were similar in both groups. The authors found no difference between groups in the primary endpoint measure of 28-day mortality or in the frequency of major organ dysfunction. However, patients treated with VP did exhibit increases in creatinine clearance and urinary output. Furthermore, in subgroup analyses, VP exhibited treatment benefit among patients with less severe sepsis (based on norepinephrine infusion $<15$ \mu g/min at enrollment) as well as in those at risk of renal dysfunction (based on Brussels organ dysfunction criteria, serum creatinine $\geq 2.0$ mg/dL).\textsuperscript{155}
Acting on the knowledge that VP enhances corticotropin responsiveness and that patients in shock states often exhibit relative adrenal insufficiency, Russell et al. recently evaluated the impact of concomitant VP and corticosteroid therapy in septic patients. In a post hoc analysis of data from the Vasopressin and Septic Shock Trial, the authors found a statistically significant reduction in mortality at 28 days among patients treated with the combination of corticosteroids and VP as opposed to corticosteroids and norepinephrine (35.9% vs 44.7%, $p = 0.03$). Equally interesting was the finding that among patients who did not receive corticosteroid therapy, those treated with VP had a higher rate of mortality compared with those who received norepinephrine (33.7% vs 21.3%, $p = 0.06$). The authors found that patients treated with corticosteroids had a substantially greater increase in plasma VP levels relative to those who did not receive steroid therapy, which they hypothesized might account for the difference in therapeutic response to VP among study groups. Although corticosteroid treatment was not randomized in this study, the results offer compelling evidence of an interaction between corticosteroids and VP in patients with shock and imply the need for further studies on the use of combination therapies in the management of these patients.

In Europe, research has been performed using the synthetic VP analog TP in the treatment of patients in septic shock. O’Brien et al. first reported the successful use of TP in 8 septic patients with refractory hypotension despite traditional therapies. Subsequent reports, including a randomized, prospective trial, confirmed these findings. A recent trial has been conducted comparing continuous infusion TP with norepinephrine or VP as first-line therapy in the treatment of patients with resuscitated septic shock. Preliminary reports suggest no harm and possibly some benefit from TP treatment. A prospective, randomized clinical trial is currently underway to identify the optimal TP dose for this indication (TESTT-I).

Data are extremely limited on the impact of VP or TP on the outcome of pediatric patients with septic shock. Based on the few published case reports, VP deficiency appears to play a lesser role in the pathophysiology of septic shock in the pediatric population compared with adults; however, VP and its analogs have in select cases resulted in some benefit. Until more research is performed, it seems reasonable to cautiously advise the use of VP or TP as rescue therapy in pediatric patients with refractory shock. Reported doses have varied widely. For TP, boluses as low as 7 μg/kg every 12 hours and 2 to 20 μg/kg every 4 hours have been used; however, continuous infusions using doses as high as 10 to 20 μg/kg/h also have been reported. When VP has been used, bolus doses of 0.01 to 0.3 U/kg or continuous infusions of 0.0002 to 0.004 μg/kg/min appear to be most common with dose titration to effect.

In summary, the preferred treatment of vasodilatory shock caused by sepsis remains unknown. Whether a single approach is appropriate for all patients is also unclear. Studies to date emphasize the value of early pharmacologic intervention to support arterial blood pressure and organ perfusion, and the potential benefit of combination therapy is under active investigation. Although more research remains to be done, low-dose VP (0.01-0.04 U/min) is now commonly used in the management of septic patients and is endorsed by international sepsis treatment guidelines.

Cardiac Arrest

Although epinephrine has been the mainstay of pharmacologic therapy for cardiac arrest, longstanding concerns over the drug’s adverse profile (eg, increased myocardial oxygen demand, arrhythmogenic potential, and postresuscitation hypertension) have motivated research into alternative therapies. Recognizing VP as an important vasoactive hormone in the body’s intrinsic neuroendocrine stress response, in the 1990s, interest in the potential role of VP in the setting of cardiac arrest heightened. Lindner et al. were the first to report that patients in cardiac arrest exhibited high levels of circulating VP and, furthermore, that substantially higher levels of the hormone were present in survivors compared with nonsurvivors. Subsequent animal studies suggested that the exogenous administration of VP in cardiac arrest improved vital organ perfusion, neurologic outcomes, and short-term survival.

Studies in human cardiac arrest patients have not consistently shown benefit from VP therapy; however, there also has not been convincing evidence of demonstrable harm. On this basis, in its updated advanced cardiac life support guidelines released in 2000, the American Heart Association (AHA) acknowledged the use of 40 U of intravenous VP as an alternative to either the first or second dose of epinephrine in the context of pulseless ventricular fibrillation or ventricular tachycardia. In 2005, AHA guidelines were revised to support the use of VP in all cases of pulseless cardiac arrest. Guidelines of the European Resuscitation Council (ERC) echo this recommendation (Table 2).

As with research in the treatment of septic shock, interest in the potential benefit of combination therapy to treat cardiac arrest soon followed. Initial studies suggested a possible survival benefit with the combined use of epinephrine and VP. Subsequently, a large-scale randomized, controlled trial involving nearly 3,000 patients with out-of-hospital cardiac arrest compared injection of 1 mg of epinephrine and 40 U of VP to 1 mg of epinephrine and saline placebo. The study failed to identify a benefit from the addition of VP in any of the measured endpoints, which included return of spontaneous circulation, neurologic outcome at discharge, and out-of-hospital and 1-year survival. More recently, a randomized, placebo-controlled study involving 100 patients with refractory in-hospital cardiac arrest found that the addition of intravenous corticosteroids to VP and epinephrine conferred a survival benefit.

Information regarding the use of VP in pediatric cardiac arrest is extremely limited. Some early reports suggested a benefit. However, a recent analysis identified worse outcome with respect to return of spontaneous circulation but no difference in the rate of hospital discharge with the use of VP. These results may be biased by the tendency for VP to be used as a “last resort” among patients with prolonged arrest and those with more significant underlying pathology. Therefore, although VP may be part of the armamentarium for the treatment of pediatric cardiac arrest, there is too little research at
this time to endorse its routine use, and, as such, the use of VP does not appear in the AHA’s algorithm for the management of pulseless arrest in pediatric patients. However, based on published reports, when used for this indication, VP doses of 0.4 U/kg and TP doses of 15 to 20 μg/kg have been suggested.

Research on treatments for cardiac arrest is fraught with complications; lack of patient homogeneity and study setting (eg, in-hospital v out-of-hospital arrest) complicate the comparison of study results. Furthermore, it is difficult to judge what amount of investigational research and/or clinical experience should constitute grounds for a change in routine patient management. In fact, because studies on VP in the setting of cardiac arrest are mixed, the AHA and ERC’s decisions to include VP on advanced cardiac life support algorithms have in fact been met with circumspection. For one, critics emphasize the high cost of VP relative to epinephrine (a single VP dose is approximately 15 times more expensive than that of epinephrine) as well as the additional cost and complications associated with arming emergency medical response personnel and in-hospital “crash carts” with both drugs. Revisions to the AHA and ERC’s guidelines are expected within the next 2 to 3 years, and it remains to be seen whether VP will keep its place on the resuscitation algorithms endorsed by these organizations.

Hemorrhagic Shock
Given VP’s known effectiveness in controlling gastrointestinal hemorrhage, several researchers have applied VP or its analogs to the management of patients presenting with trauma-induced hemorrhagic shock. Voelckel et al reported enhanced renal perfusion and postresuscitation hemodynamic stability in pigs treated with conventional CPR plus VP compared with CPR plus epinephrine after experimentally induced hypovolemia and cardiac arrest. Subsequently, in a similar experimental model, the same group reported favorable results with the use of VP as first-line therapy for uncontrolled hemorrhagic shock when compared with either fluid or epinephrine therapy alone. Several case reports have acknowledged a favorable impact with VP as a temporizing measure to support blood pressure and reduce resuscitative fluid requirements, this benefit may come at the expense of adverse metabolic and hemodynamic consequences, including lactic acidemia and a decline in cardiac index. Currently, a multicenter, randomized controlled trial, the Vasopressin in Traumatic Hemorrhagic Shock (VITRIS) trial, is being organized in Europe to investigate the impact of VP in the prehospital management of uncontrolled hemorrhagic shock. It is expected that the results of this trial will help form more definitive recommendations on the use of VP in the context of hemorrhagic shock.

Anesthesia-Induced Hypotension
Under ordinary circumstances, arterial blood pressure is maintained through the complementary action of the (1) SNS, (2) RAAS, and (3) vasopressinergic response. VP’s role in correcting hypotension is in essence an emergency mechanism that manifests when other systems fail or are overwhelmed. Conventionally used agents for both general and neuraxial anesthesia alter the SNS response to hypotension. Evidence suggests that epidural anesthesia also impairs the renin response to hypotension via the blockade of renal SNS discharge. Much of the hypotension induced by anesthetics is catechol responsive, as shown by the effective use of vasoconstrictors such as phenylephrine and ephedrine to treat anesthesiainduced vasodilation. However, clinical experience suggests that at least some of the hypotension induced by anesthesia is refractory to catecholamines. In dogs, sympathetic blockade caused by epidural anesthesia has been shown to induce a compensatory rise in endogenous VP secretion. In humans, the exogenous administration of VP has been used successfully to treat catechol-resistant hypotension. VP appears to be particularly useful in treating hypotension in anesthetized patients who also are treated with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers because these patients suffer from concomitant SNS and RAAS dysfunction.

VP also has been used successfully in the management of cardiovascular collapse because of anaphylaxis occurring under general anesthesia. Schummer et al reported the successful use of VP for this indication in 7 patients whose hypotension was refractory to conventional catecholamine treatment including epinephrine and norepinephrine. The authors suggested that VP in this context may in addition to its vasoconstricting effect also exert anti-inflammatory action by blunting NO production.

Postcardiotomy/Cardiopulmonary Bypass–Induced Hypotension
It has been estimated that approximately 10% of cardiac surgery patients experience vasodilatory hypotension that is not explained by primary myocardial dysfunction or sepsis. Extracorporeal circulation or cardiopulmonary bypass induces hemostatic derangements that make patients especially prone to postoperative blood loss. Relative depletion of coagulation factors and fibrinogen as well as platelet dysfunction contribute to this condition. Additionally, cytokine release induced by endothelial injury induces vasodilation that exacerbates the hemodynamic impact of postoperative blood loss.

Patients undergoing cardiac surgery also experience significant fluctuations in serum VP concentrations. The initiation of cardiopulmonary bypass (CPB) is associated with a dramatic rise in serum VP levels; this is followed by a gradual return to baseline in the postoperative period. In some patients, VP levels are inappropriately low relative to the degree of postoperative hypotension and contribute to refractory vasodilatory shock. Risk factors for the development of post-CPB vasodilatory hypotension include low presurgical ejection fraction and the use of ACE inhibitors. In these patients, exogenous VP infusion has been found to effectively increase mean arterial pressure (MAP) and reduce catecholamine requirements. Furthermore, in a double-blind, randomized trial, prophylactic VP infusion begun before the initiation of CPB was shown to improve hemodynamic stability in patients undergoing coronary artery bypass graft surgery or valvular surgery who also were treated with ACE inhibitors. De-
increases in time to extubation and length of intensive care unit stay also were observed.

Dunser et al.219 investigated the impact of VP infusion among 41 patients with catechol-resistant postcardiotomy shock. They found that VP infusion was associated with significant increases in MAP, left ventricular stroke work index, and systemic vascular resistance along with a decrease in heart rate and no change in cardiac index or stroke volume index.219 These results have been substantiated by other studies.218,220

The unique benefits and risks of VP therapy to treat vasodilatory hypotension remain to be fully established. Some groups have identified a reduction in markers of myocardial ischemia associated with VP infusion.205,221 In a swine model, at low flow rates such as those used during CPB, Mayr et al.222 found that VP improved coronary artery flow blood and did not increase coronary vasoconstriction and produce a substantial negative inotropic effect.224,225 The use of VP in patients with cardiogenic as opposed to vasodilatory hypotension is likely to pose the most risk of exacerbating myocardial dysfunction.

There is also evidence to suggest that VP therapy may confer a renal-protective effect. VP infusion initiated in patients with refractory post-CPB hypotension has been shown to increase urine output,218 and the use of VP to treat hypotension after left ventricular assist device insertion has resulted in improved recovery of renal function.226 On the other hand, VP is a potent splanchnic vasoconstrictor and may promote gastrointestinal ischemia in at-risk patients. VP also increases platelet aggregation, which could promote thrombogenesis and impair microcirculation. However, no data suggest that these complications are common.

Several vasopressors in addition to VP, including norepinephrine, phenylephrine, and methylene blue, have been shown to increase MAP in postcardiotomy hypotension. To date, there is insufficient evidence to suggest the use of one exclusive agent.227 However, existing data clearly place VP among the therapeutic options.

Other Shock States

Evidence from case reports has offered the use of VP or its analogs as rescue therapy in other conditions associated with refractory hypotension including overdoses of calcium channel blockers,228 and tricyclic antidepressants229 as well as traumatic brain injury.228 By virtue of their sporadic occurrence, evidence of the efficacy of VP and VP analogs for these unusual circumstances will remain anecdotal.

The explanation for why VP successfully reverses catecholamine-refractory vasodilation is not firmly established, but several hypotheses have been offered. Both catecholamines and VP exert some of their vasoconstrictive effects by increasing intracellular calcium in vascular smooth muscle cells. In addition, however, VP blocks cyclic guanosine monophosphate-mediated vasodilation produced by inflammatory mediators such as interleukin 1, ANP, and NO.209,231–233 VP also inhibits adenosine triphosphate–mediated potassium channel activation on vascular smooth muscle cells, which improves vascular responsiveness to catecholamine therapy.234–238 Vascular tone also may be restored by virtue of VP-mediated release of cortisol.239 The existence of these multimodal mechanisms likely explains the effectiveness of VP therapy in shock states of various etiologies.

Other Applications

Several nonpeptide VP antagonists are in various stages of clinical trials for a wide assortment of clinical indications. V1-receptor antagonists including relcovaptan are under investigation for the management of Raynaud’s disease,240 premature labor,241,242 dysmenorrhea,243,244 and Meniere’s disease.245 V1-receptor antagonists also are offering new potential in reducing cortisol levels in patients with ACTH-independent forms of Cushing syndrome caused by aberrant adrenocortical receptors.246

The finding that cyclic adenosine monophosphate promotes renal epithelial cell growth has prompted investigations on the utility of V2-receptor antagonist therapy for slowing the progression of renal dysfunction in patients with polycystic kidney disease.247–255 Studies of V2-receptor antagonists for other indications including the reduction of intraocular pressure in patients with glaucoma256,257 and the minimization of cerebral edema and infarct size after ischemic brain injury256,258–261 are also underway.

In the neuropsychiatric arena, V3 antagonist therapy has shown promise in reducing stress-induced cortisol secretion and exerting anxiolytic and mood-elevating effects in rodent models.262–277 SSR-149415, the only orally active V3-receptor antagonist, is currently in phase II clinical trials to evaluate its efficacy in humans (Table 2).

ADVERSE EFFECTS OF DRUG THERAPY

VP and VP Analogs

Splanchnic Perfusion

Despite its beneficial role, significant adverse effects have been reported with both VP and its analogs. Although VP redistributes blood flow to vital organs, it does so in part at the expense of splanchnic and peripheral tissue perfusion. As such, VP has been observed to induce skin necrosis and severe limb ischemia, particularly when administered through peripheral veins.162,278–282 A decrease in bile flow and increases in bilirubin and transaminase levels also have been reported.158,220,223,283 Experimental models have produced conflicting results on the effect of VP or V1 agonists on gut microcirculation; some groups have measured an increase in the mucosal-arterial PCO2 gradient, implying the potential for impaired mesenteric circulation.24,278–286 However, this result has not been consistently duplicated.285,287 The potentially deleterious effect of VP on splanchnic perfusion seems keenly influenced by the overall fluid status of the patient when therapy is initiated; VP administered in the context of hypovolemia appears particularly detrimental, whereas VP in fluid-resuscitated states may result in net improvement in splanchnic hemodynamics.288 There are similar conflicting reports on the effects of VP on coronary vessels; but acute myocardial ischemia has been observed particularly with bolus dosing of TP.224,289
Cardiac Index

Concern also has been raised that VP may worsen post-resuscitation acidemia and increase the risk of reperfusion injury-induced multiorgan system dysfunction, despite improving arterial blood pressure and limiting resuscitative fluid volume requirements.\textsuperscript{191,192} Although VP therapy may restore blood pressure, depression of cardiac index has been observed.\textsuperscript{24,146,158–160,203,223,286,290} However, this impact seems to vary based on initial cardiac index. Specifically, Luckner et al.\textsuperscript{223} showed that although VP decreased the cardiac index in patients with initially elevated cardiac indices, it had little effect in patients whose cardiac index was normal at the start of therapy and actually improved cardiac indices in patients with low starting values. This has led investigators to speculate that the change in cardiac index observed with VP therapy may represent an appropriate adaptive response to blood pressure normalization rather than a pathologic effect on myocardial function.\textsuperscript{40}

Hemostasis

The activation of V1 receptors increases intracellular calcium and promotes platelet aggregation. V2-receptor stimulation promotes coagulation via release of vWF and plasminogen activator. Theoretically, these hemostatic effects may compromise microcirculation, promote thromboembolism, and/or cause bleeding complications related to thrombocytopenia. Although some groups have observed a drop in platelet count with VP therapy and actually improved cardiac indices in patients with low starting values. This has led investigators to speculate that the change in cardiac index observed with VP therapy may represent an appropriate adaptive response to blood pressure normalization rather than a pathologic effect on myocardial function.\textsuperscript{40}

Fluid and Electrolyte Balance

Although VP is known to possess antidiuretic properties via V2 receptor activation in the kidneys, in the setting of septic shock, VP and VP analog therapy consistently have been shown to increase urinary output.\textsuperscript{140,155} Hyponatremia is a rare event and only seems to be of concern when high-dose therapy is used.\textsuperscript{289}

In summary, the pathophysiology of shock and the traditional catecholamine therapy used to treat it often entail organ-specific compromise; as such, patient prognosis is grim a priori. Although conflicting reports have been published, there is no convincing evidence from human studies to suggest that adverse consequences occur in excess among patients treated with VP or its analogs. Therefore, although definitive guidelines remain forthcoming, VP and VP analog therapy have earned deserved roles in the treatment armamentarium of catecholamine-refractory shock.

VP Antagonists

Relatively few adverse effects have been identified with VP antagonist treatment. In animal models, conivaptan has been associated with fetal malformations at subtherapeutic levels and has delayed labor onset in pregnant rats. It is therefore to be avoided in pregnancy. Conivaptan also substantially alters the concentrations of many concomitantly administered drugs because of its powerful inhibition of the CYP3A4 enzyme. For this reason, it is only available in parenteral form, and the recommended duration of therapy is limited to 4 consecutive days.\textsuperscript{56,59,73,97}

Thirst, dry mouth, polyuria, and overrapid correction of hyponatremia are among the more common side effects observed with the vaptans. They are usually only clinically relevant when high-dose therapy is used in conjunction with fluid restriction.\textsuperscript{53,57,59}

CONCLUSION

Vasopressin is a homeostatic neuroendocrine hormone whose chief role is to maintain plasma osmolality. Although important in health, in the study of disease states, the breadth of VP’s functional repertoire, now known to include regulation of vascular tone, alteration of blood coagulability, modulation of mood, and stress activation, has become apparent. Relative VP depletion or abundance has been shown in multiple pathologic states, making VP agonist and antagonist therapies exciting targets of study in fields as disparate as psychiatry and critical care medicine. The extent to which these therapies may improve patient outcomes and alter the natural history of disease remain questions for ongoing research.

REFERENCES


120. Cattaneo M: The use of desmopressin in open-heart surgery. Haemophilia 14:40-47, 2008 (suppl 1)


266. Landgraf R: The involvement of the vasopressin system in stress-related disorders. CNS Neurol Disord Drug Targets 5:167-179, 2006


