Vasopressin and its antagonists: what are their roles in acute medical care?

Otherwise known as antidiuretic hormone, vasopressin is a small polypeptide of nine amino acids produced in the hypothalamus and secreted from the posterior pituitary gland. It was first identified more than 100 yr ago as a potent vasopressor. After production of a synthetic analogue in 1954 (for which Vincent Du Vigneaud from Cornell University, USA, received a Nobel Prize), high doses were found to produce coronary artery vasoconstriction. Until recently, vasopressin was largely used only as an antidiuretic agent to treat diabetes insipidus, but it is now being used as a vasopressor in a variety of disease states.

The most important physiological role of endogenous vasopressin is in control of fluid balance. Vasopressin is released when the sensitive osmoreceptors in the hypothalamus detect very small increases in extracellular fluid osmolality (mean threshold value 280 mOsm kg$^{-1}$). It increases water reabsorption through the collecting ducts of the nephron. In contrast, a much less sensitive trigger for vasopressin release is hypovolaemia—a 10% decrease in arterial volume sensed by baroreceptors in the aortic arch and carotid sinus is needed to stimulate vasopressin release.

Vasopressin acts at three types of vasopressin (V) receptor which all work via G proteins. $V_{1a}$ receptors, found in smooth muscle and the heart, are primarily responsible for the vasoconstrictive properties of vasopressin. $V_2$ receptors lie within the collecting ducts of the nephron and are involved in water reabsorption. $V_{1b}$ receptors (also known as $V_3$ receptors), found within the central nervous system, are involved in the secretion of corticotrophin-releasing hormone.
When is vasopressin useful?

Organ donation

In the 1980s, organ donation teams recognized that although vasopressin was an effective treatment for diabetes insipidus, it also helped preserve organ function and reduced inotrope requirements in brain-dead patients before surgery. The Intensive Care Society guidelines for adult organ and tissue donation recommend that hormonal replacement therapy (a bolus of methylprednisolone with an infusion of vasopressin and an infusion of either triiodothyronine or l-thyroxine) should be considered in all organ donors (www.uktransplant.org.uk). Hormonal resuscitation is associated with a significant increase in the numbers of organs transplanted per donor, and is now routine practice in the UK.

Cardiac arrest

In 1996, it was noted that survivors of cardiac arrest had increased levels of vasopressin and cortisol compared with non-survivors, which inspired studies into the use of vasopressin during cardiac arrest. Various studies have looked at differences in outcome between the use of epinephrine or vasopressin alone. The results are inconclusive and a subsequent review, including a detailed meta-analysis, concluded that there was no benefit in using vasopressin over epinephrine. Studies are underway of vasopressin combined with epinephrine in cardiac arrest. The current American Heart Association Guidelines for cardiopulmonary arrest include vasopressin (40 iu i.v.) as an alternative to the second dose of epinephrine, but the UK Resuscitation Council advises the continued use of epinephrine 1 mg i.v. every 3–5 min. The use of vasopressin in cardiac arrest remains controversial and, until more convincing evidence is produced, we probably should not change our practice.

Sepsis

Why choose vasopressin over other vasoconstrictors in sepsis? Studies have shown a relative vasopressin deficiency after 36 h in hypotensive septic patients, and reduced vasopressin responsiveness has been shown in septic rats. Vasopressin increases plasma cortisol levels probably by enhancing release of corticotrophin-releasing factor. Clinicians at present use steroids in sepsis: this probably by enhancing release of corticotrophin-releasing factor. A bolus of methylprednisolone with an infusion of vasopressin and an infusion of either triiodothyronine or l-thyroxine should be considered in all organ donors (www.uktransplant.org.uk). Hormonal resuscitation is associated with a significant increase in the numbers of organs transplanted per donor, and is now routine practice in the UK.

Importantly, vasopressin has a beneficial effect on renal blood flow: animal studies in sepsis show an improved creatinine clearance and a preservation of renal function compared with norepinephrine.

Vasopressin is acknowledged in the Surviving Sepsis Campaign as an adjunct vasopressor in catecholamine-resistant shock states. In sepsis, doses no greater than 0.04 iu min⁻¹ should be used, as higher doses have been shown to produce myocardial ischaemia and cardiac arrest.

In the UK, vasopressin is often used to restore mean arterial pressure (MAP) in septic patients when high doses of conventional inotropes and vasopressors have failed. Perhaps we should use vasopressin at an earlier stage in these patients? Would this improve morbidity and survival? Results from the recent Vasopressin and Septic Shock Trial (VASST) suggest that low-dose vasopressin added to conventional vasopressors may be more effective than supplementary norepinephrine in reducing mortality, but only in less severe septic shock. Interestingly, the patients who received vasopressin were given more dobutamine and milrinone than the no-vasopressin group.

Terlipressin is a longer-acting (half-life 6 h) synthetic analogue of vasopressin which has been shown to have beneficial haemodynamic effects in patients with septic shock who are unresponsive to conventional vasopressors. Although routinely given in hepatorenal syndrome, the use of terlipressin in patients with sepsis requires further clarification of its dose requirements, side-effects, and efficacy.

Haemorrhagic shock

One of the most interesting uses of vasopressin is in hypovolaemic shock. Animal studies have shown improved short-term survival with vasopressin compared with placebo in refractory haemorrhagic shock. Raedler and colleagues studied 21 pigs after severe liver injury in three groups, which received either saline, vasopressin 0.4 iu kg⁻¹, or fluid resuscitation (Ringer’s lactate 1000 ml and hetastarch 1000 ml). No other vasoconstrictor was given. Thirty minutes later, any surviving pigs were resuscitated with fluids and the bleeding controlled surgically. MAP in the vasopressin group 5 min post-treatment was significantly higher than that in the placebo or fluid resuscitation group (MAP=58 mm Hg; MAP=7 mm Hg; MAP=32 mm Hg, respectively). All pigs treated with vasopressin survived to surgery and for a further 60 min, but in the other groups, all the pigs died.

Several case reports have recorded Level 3 evidence of success with vasopressin during hypovolaemic shock which was unresponsive to conventional fluids, blood, and vasopressors. A multicentre, randomized controlled trial is soon to start, studying the effects of vasopressin compared with placebo in humans with refractory haemorrhagic shock (www.vitris.at). Many clinicians use it when other...
inotropes have failed to have an effect in hypovolaemic patients, despite the lack of Level 1 or 2 evidence.

**Anaesthesia for neuroendocrine tumours**

Rarely, removal of a phaeochromocytoma may be complicated by severe hypotension resistant to catecholamine treatment. Several case reports have reported the successful use of vasopressin in these circumstances.

Clinical indications and evidence for the use of vasopressin are summarized in Table 1.

**Vasopressin antagonists**

Vasopressin antagonists promote the excretion of electrolyte-free water—known as **aquaresis**. Three of the selective vasopressin-receptor antagonists undergoing Phase 3 trials are tolvaptan, conivaptan, and lixivaptan. Tolvaptan and conivaptan are benzazepine derivatives. Tolvaptan and lixivaptan have high specificity for the V2 receptor (tolvaptan has a 10-fold affinity and lixivaptan a 100-fold affinity for V2 compared with V1a), whereas conivaptan is known as a combined V1/V2 receptor antagonist (it has a 10-fold greater affinity for the V1a receptor). These drugs are also inhibitors of the liver enzyme cytochrome P450 3A4. Conivaptan is the most potent, and it should not be prescribed with other cytochrome P450 3A4 inhibitors such as clarithromycin. Concurrent use of conivaptan with drugs that are metabolized by cytochrome P450 3A4 (e.g. 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, such as simvastatin) has the potential for increased drug plasma concentrations and side-effects. To minimize drug interactions in the community, the USA Food and Drug Administration (FDA) has only approved conivaptan for use as an i.v. preparation. Tolvaptan and lixivaptan have much less effect on cytochrome P450 3A4 and are being developed in oral preparations. The uses and doses of these vasopressin antagonists are summarized in Table 2.

**Heart failure**

High circulating levels of vasopressin are found in patients with left ventricular dysfunction, even when they are asymptomatic. Chronic V1a receptor stimulation combined with peripheral vasoconstriction increasing afterload may reduce left ventricular function. Vasopressin stimulation of V2 receptors compounds the problem, increasing fluid retention and preload. Hyponatraemia often accompanies the water retention and has been shown to be a marker of severe disease. The use of diuretics in the treatment of heart failure is associated with electrolyte abnormalities and impaired renal function. Vasopressin antagonists could provide an alternative to diuretic therapy in these patients.

The Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST) trial reported in March 2007 showed no effect on mortality or heart failure-related morbidity with tolvaptan compared with placebo. However, this study did show an increase in urine output, a reduction in body weight and oedema, and a normalization of serum sodium values in these patients. Conivaptan has also been studied in congestive heart failure. Given i.v., it reduced pulmonary capillary wedge pressures and right atrial pressures within 3–6 h and increased urine output. As yet, no improvements in long-term clinical status or mortality have been reported with this group of drugs. The only FDA-approved indication for the use of vasopressin antagonist therapy (just conivaptan at present) is in the treatment of euvoalaemic and hypervolaemic hyponatraemia.

**Hyponatraemia**

Hyponatraemia (generally defined as a plasma sodium concentration <135 mmol litre\(^{-1}\)) is one of the most

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**Table 1** Indications and evidence for the use of vasopressin. Extracted with permission from Treschan and Peters

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<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Evidence</th>
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<tbody>
<tr>
<td>As part of hormonal resuscitation in organ donation patients</td>
<td>Cardiac arrest</td>
<td>0.5–4.0 iu h(^{-1})</td>
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<td></td>
<td>Second dose of epinephrine</td>
<td>40 iu i.v. to replace second dose of epinephrine</td>
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<tr>
<td>Congestive heart failure</td>
<td>Triphasic</td>
<td>0.01–0.04 iu min(^{-2})</td>
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<td></td>
<td>Anaesthesia for neuroendocrine tumours</td>
<td>Bolus dose (from 0.4 to 20 iu) and infusion up to 0.1 iu min(^{-1})</td>
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**Table 2** Indications and evidence for the use of vasopressin antagonists

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<th>Indication</th>
<th>Dose</th>
<th>Evidence</th>
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<tr>
<td>Hyponatraemia</td>
<td>Conivaptan 20 mg i.v. once daily</td>
<td>Trial showing efficacy, has FDA approval</td>
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<td></td>
<td>Tolvaptan 15–60 mg p.o. once daily</td>
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<tr>
<td></td>
<td>Conivaptan 10–40 mg i.v. once daily</td>
<td>Reduced RAP and wedge pressure</td>
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<td></td>
<td></td>
<td>Reduction in dyspnoea and oedema, no reduction in mortality demonstrated</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Tolvaptan 30 mg p.o. once daily</td>
<td>Effective at reducing cyst volume in animal studies, human study underway (<a href="http://www.clinicaltrials.gov/ct/show/NCT00428948">www.clinicaltrials.gov/ct/show/NCT00428948</a>)</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>Tolvaptan</td>
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common electrolyte disorders encountered in hospital patients. It is a risk factor for death in heart failure and cirrhotic patients.23 27 Longstanding mild hyponatraemia has been associated with impaired gait and recurrent falls, but with plasma sodium levels <120 mmol litre$^{-1}$, more serious neurological symptoms such as lethargy, seizures, and coma can occur. The rate of decrease in serum sodium, rather than the absolute value reached, produces many of these symptoms as the expanding cells in the central nervous system struggle to cope with the rapid changes in osmolarity. Hyponatraemia is classified into hypovolaemic (as in gastrointestinal loss), euvoalaemic (as in syndrome of inappropriate antidiuretic hormone secretion and postoperative hyponatraemia), and hypervolaemic (as in cirrhosis and cardiac failure). It can be difficult to treat, especially in cardiac and liver failure patients. Current treatments for hyponatraemia such as fluid restriction can be ineffective and poorly tolerated.28 Correction of low serum sodium levels must be carefully controlled. The aim should be to increase levels by no more than 0.5 mmol litre$^{-1}$ h$^{-1}$ to avoid the possibility of myelinolysis.29

In hyponatraemia, the primary problem is generally not a lack of sodium but an excess of water. Vasopressin release subsequent to arterial underfilling (as is seen in heart failure and alcoholic cirrhosis) leads to increased water reabsorption in the majority of hyponatraemic patients.30 Both the V$_2$ and the combined V$_1$/V$_2$ receptor antagonists have been shown to treat hyponatraemia without causing electrolyte disturbances or renal failure.31

Tolvaptan has been shown to treat hyponatraemia in euvoalaemic and hypervolaemic patients more effectively than placebo.28 These studies were mostly in outpatients with a starting dose of 15 mg orally once daily titrated up to 60 mg as necessary. Plasma sodium concentration began to increase within 8 h of receiving tolvaptan and remained elevated throughout the 30 day study period, decreasing after stopping the drug. Over-correction was rare—plasma sodium was greater than 146 mmol litre$^{-1}$ in only four of 223 patients receiving tolvaptan. Side-effects of the drug included thirst and a dry mouth, and serious adverse events occurring in eight patients included dehydration, hypotension, and syncope.

The efficacy of conivaptan in the treatment of hyponatraemia has been successfully demonstrated,31 and it has received FDA approval for the treatment of euvoalaemic and hypervolaemic hyponatraemia in hospitalized patients.

These drugs are not yet available for use in the UK. The benefits of vasopressin antagonists in perioperative care remain unknown, but have considerable potential for the future, particularly for the management of hyponatraemia and heart failure.

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References
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