Therapeutic role of vasopressin receptor antagonism in patients with liver cirrhosis

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ABSTRACT

Vasopressin, or antidiuretic hormone, is a peptide hormone that is released from the posterior pituitary gland in response to changes in blood pressure and plasma osmolality. The main pathophysiological states associated with high plasma vasopressin concentrations are cirrhosis, cardiac failure and syndrome of inappropriate antidiuretic hormone (SIADH) secretion. Pharmacological treatments for disorders of excess vasopressin secretion have been limited. However, oral bio-available selective and non-selective V₁ and V₂ receptor antagonists have recently become available for clinical use. Water retention in cirrhosis is a common problem, leading to ascites, peripheral oedema and hyponatraemia. Raised plasma vasopressin concentrations and decreased delivery of glomerular filtrate are believed to be the most important factors in the development of water retention. V₂ receptor antagonists are aquaretic agents that promote water excretion and improve hyponatraemia. Their potential role in cirrhosis has been examined in a number of recent studies that have shown increased free water clearance and serum sodium concentrations with few adverse effects. V₂ receptor antagonists represent a novel and promising new class of agent that may have major clinical utility in the treatment of patients with liver cirrhosis.

INTRODUCTION

Vasopressin is a peptide hormone with major cardiovascular and renal effects (Figure 1). Patients with liver cirrhosis often have derangements in water handling that lead to ascites, peripheral oedema and hyponatraemia [1], and result from raised plasma concentrations and decreased delivery of glomerular filtrate in the kidney. Pharmacological manipulation of the up-regulated vasopressin system has previously been ineffective [2], but vasopressin receptor antagonists have recently become available for clinical use [3,4].

In this article, we will describe the vasopressin system and review the pharmacological approaches to manipulating this homeostatic pathway. We will specifically explore the rationale and early clinical experience of V₂ receptor antagonists in liver cirrhosis:

Key words: antagonist, aquaporin, aquaretic, cirrhosis, vasopressin.

Abbreviations: SIADH, syndrome of inappropriate antidiuretic hormone; ACTH, adrenocorticotropic hormone (corticotropin).
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and the paraventricular nucleus [7,8]. The precursor, preprovasopressin, is cleaved into a three-domain prohormone by removal of a signal peptide [9]. This prohormone is stored in secretory granules containing endopeptidase, exopeptidase, mono-oxygenase and lyase activities. These enzymes act sequentially on the prohormone to produce arginine-vasopressin, neurophysin II and glycopeptide (Figure 2) [9]. Genetic mutations in either the signal peptide or neurophysin II give rise to central diabetes insipidus [10]. Neurophysin II is essential for the proper folding and sorting of the prohormone complex from the endoplasmic reticulum to the secretory granule [10].

Increased plasma osmolality and hypovolaemia are the principal physiological stimuli for vasopressin secretion, although other hormones, neurotransmitters and pharmacological agents can either induce or inhibit vasopressin release (Table 1) [6]. Peptidases, particularly those found in the kidney and liver, inactivate circulating vasopressin, resulting in a short plasma half-life of ~25 min [6].

**Receptors**

Three known receptor subtypes mediate the actions of vasopressin: \( V_1 \) (\( V_{1a} \)), \( V_2 \) and \( V_3 \) (\( V_{1b} \)) receptors [11]. The \( V_1 \) receptor is G-protein-coupled and operates via the phosphoinositide signalling pathway, causing release of intracellular \( \mathrm{Ca}^{2+} \) ions. It is found in vascular smooth muscle cells, hepatocytes and platelets [7], where it mediates vasoconstriction, glycogenolysis and platelet aggregation respectively. The \( V_2 \) receptor is also coupled to a G-protein, but operates via the adenylate cyclase pathway, utilizing cAMP as its second messenger. Although it was originally thought to be present only in the kidney, recent studies have shown \( V_2 \) receptor effects in other organs, including the endothelium [12]. The \( V_3 \) (\( V_{1b} \)) receptor acts through the phosphoinositide pathway and is found predominantly in the anterior pituitary. Stimulation of the \( V_1 \) receptor leads to release of adenocorticotropic hormone (ACTH).

**Physiology**

The release of vasopressin is regulated by baroreceptors and osmoreceptors, which detect decreases in blood pressure and increases in extracellular Na\(^+\) concentration.
Table 1 Stimulators and inhibitors of vasopressin secretion

<table>
<thead>
<tr>
<th>Hormones/neurotransmitters</th>
<th>Pharmacological agents</th>
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<tr>
<td><strong>Stimulate:</strong></td>
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<tr>
<td>Acetylcholine (nicotinic)</td>
<td>Vincristine</td>
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<tr>
<td>Histamine (H1)</td>
<td>Cyclophosphamide</td>
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<td>Dopamine (D1 and D2)</td>
<td>Tri cyclic antidepressants</td>
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<td>Glutamine</td>
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<td>Aspartate</td>
<td>Adrenaline</td>
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<td>Cholecystokinin</td>
<td>High-dose morphine</td>
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<td>Neuropeptide Y</td>
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<td>Substance P</td>
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<td>Vasoactive intestinal polypeptide</td>
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<td>Prostaglandins</td>
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<td>Angiotensin II</td>
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<td><strong>Inhibit:</strong></td>
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<tr>
<td>Atrial natriuretic peptide</td>
<td>Ethanol</td>
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<tr>
<td>γ-Aminobutyric acid</td>
<td>Phentoin</td>
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<td>Opioids (Kappa receptors)</td>
<td>Low-dose morphine</td>
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<td></td>
<td>Glucocorticoids</td>
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<td>Fluphenazine</td>
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<td>Haloperidol</td>
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<td>Butorphanol</td>
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<td>Oxilorphon</td>
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respectively. There is a very sensitive linear relationship between plasma osmolality and vasopressin release, and this maintains the plasma osmolality within the narrow range 284–295 mosmol/l.

Vasopressin counters intravascular volume depletion and hypotension by causing water retention and arterial vasoconstriction. In the distal tubule of the nephron, vasopressin acts upon the V2 receptor and, via cAMP, activates protein kinase A. This in turn phosphorylates microtubular subunits that aggregate to form specific water channels, or ‘aquaporins’, that are inserted into the luminal membrane [13,14] (Figure 3). These membrane proteins allow the reabsorption of large volumes of water and increase body water content. Mutations in the aquaporin gene result in a form of nephrogenic diabetes insipidus [13].

Although vasopressin is a potent vasoconstrictor and pressor agent, it produces a dose-dependent biphasic response in the peripheral arterial circulation: vasoconstriction at low concentrations and vasodilatation at high concentrations [15,16]. The high-dose vasodilatory response appears to be mediated by the V2 receptors, since it is blocked by selective V2 receptor antagonism [15,17]. Moreover, patients with nephrogenic diabetes insipidus due to a V2 receptor defect demonstrate an isolated vasoconstrictor response to vasopressin and are resistant to the effects of the selective V2 agonist desmopressin [18]. This V2 receptor-mediated vasodilatory effect appears to be endothelium-dependent and mediated via nitric oxide release [19].

**Pathophysiology**

Vasopressin secretion and water retention are associated with syndrome of inappropriate antidiuretic hormone (SIADH) secretion, congestive cardiac failure and cirrhosis of the liver. SIADH is the commonest form of normovolaemic hyponatraemia, and is often secondary to malignant disease, chest disorders and central nervous system pathology.

Advanced heart failure is associated with elevated plasma vasopressin concentrations and decreased delivery of glomerular filtrate [20]. Because of a reduced cardiac reserve and output, there is systemic hypotension and underfilling of the arterial vascular compartment. This leads to peripheral vasoconstriction and neurohumoral activation, including the sympathetic nervous, renin–angiotensin–aldosterone and vasopressin systems. Similar neurohumoral effects are seen in patients with advanced liver cirrhosis; however, in contrast with heart failure, there is a hyperdynamic circulation and a high cardiac output state in association with relative intravascular volume depletion and vasodilatation.

Many studies report high plasma vasopressin concentrations in patients with decompensated cirrhosis [1,2,21–24], presumably reflecting the vasodilatation and a reduced effective intravascular volume [25]. Raised plasma vasopressin concentrations and decreased delivery of glomerular filtrate are the two most important factors implicated in the development of impaired water handling, which has an estimated prevalence of 75 % in hospitalized patients with ascites [25]. Animal studies support these clinical observations, with a linear relationship between plasma vasopressin concentration and water excretion observed in rodent models of cirrhosis [26]. Furthermore, Battleboro rats, which have a congenital vasopressin deficiency, do not develop impaired water handling with carbon tetrachloride-induced liver cirrhosis [27].

**PHARMACOLOGICAL MANIPULATION OF VASOPRESSIN**

Unlike the renin–angiotensin system, no enzymes have been found to be specifically responsible for vasopressin formation or degradation. Thus, at present, there are no enzyme inhibitors that selectively affect plasma vasopressin concentrations. The major focus, therefore, has been on identifying specific and selective vasopressin receptor agonists and antagonists.

**Vasopressin receptor agonism**

Variceal bleeding is a common and life-threatening complication of liver cirrhosis. Vasopressin reduces
Figure 3  Effects of vasopressin on the renal collecting duct cell

Vasopressin receptor antagonism

Selective V₁ receptor antagonism

At present, a role for a V₁ receptor antagonist remains to be defined. Activation of the V₁ receptor leads to peripheral vasoconstriction, and may cause myocyte and left ventricular hypertrophy, suggesting a potential role of V₁ receptor antagonism in the treatment of hypertension and congestive cardiac failure [32].

The effects of the non-peptide V₁ antagonist OPC-21268 have been examined in rats with ACTH-induced hypertension and in an ovine myocardial infarction model [33,34]. In both of these models, OPC-21268 had no beneficial effects on blood pressure or left ventricular remodelling.

SR49059 was the first orally bioavailable non-peptidic V₁ receptor antagonist to be tested in clinical studies [3,35]. In healthy volunteers, it has a good safety and tolerability profile, with no demonstrable V₂ antagonistic properties [36]. However, when given to patients with congestive heart failure or hypertension, it failed to demonstrate clinical efficacy when used as a monotherapy [35,37].

Selective V₂ receptor antagonism

Peptidic V₂ receptor-selective antagonists were initially developed by modification of the selective peptidic V₂ agonist desmopressin. They produce an effective aquarexis in animal models [38], but their use in humans was limited by agonist activity, a short plasma half-life and poor oral bioavailability [7,39–41].

The first selective non-peptidic V₂ receptor antagonist, OPC-31260, was developed 10 years ago from an analogue of the selective non-peptidic V₁ receptor antagonist OPC-21268 [4]. Since then, other non-peptidic V₂ receptor antagonists have been formulated (VPA-985, SR121463) [42] that have a greater receptor affinity than OPC-31260 [43]. These V₂ receptor antagonists have no agonist effects in humans, are orally
bioavailable and have a longer plasma half-life. VPA-985 is absorbed rapidly, and achieves maximal plasma concentrations within 1 h of ingestion [44].

In well hydrated conscious rats, V2 receptor antagonism increases urine flow and decrease urine osmolality [43,45,46]. Clinical studies (Table 2) have confirmed these effects in humans. OPC-31260 has been shown to increase urine volume in a dose-dependent fashion and increase plasma sodium concentration [47]. Importantly, there are no associated changes in systemic haemodynamic variables or potassium concentration. Indeed, direct intra-arterial administration of OPC-31260 has no effect on forearm vascular tone, suggesting that, in healthy volunteers, the V2 receptor does not contribute to basal vascular tone [17]. The maximum dose of OPC-31260 of 200 mg/kg was also associated with a 3-fold increase in the plasma vasopressin concentration, suggesting a role of the V2 receptor in either the clearance or negative-feedback regulation of vasopressin.

### Non-selective combined V1 and V2 receptor antagonism

Conivaptan (YMO87) was the first orally active non-peptidic dual V1/V2 receptor antagonist. In the rat, the aquaretic effect of 1 mg/kg conivaptan is equivalent to that of 100 mg/kg frusemide [48]. Conivaptan also causes dose-dependent inhibition of the pressor effects of exogenous vasopressin administration. Comparable effects have also been seen in clinical studies, where conivaptan had a good side-effect profile in healthy volunteers [49].

Plasma vasopressin levels may be elevated in patients with heart failure, especially when the left ventricular dysfunction is severe. Stimulation of V1 and V2 receptors leads to potentially adverse pathophysiological effects: namely vasoconstriction and myocyte hypertrophy [32], and water retention and hyponatraemia respectively. Therefore, in contrast with patients with liver cirrhosis, non-selective dual V1 and V2 receptor antagonism should be more beneficial in the treatment of patients with severe heart failure. In early clinical trials, conivaptan has been assessed as a possible adjunct to conventional heart failure therapy [50]. Its use resulted in promising haemodynamic effects, with a reduction in pulmonary capillary wedge pressure and an increase in urine output, without causing significant hypotension or tachycardia.

### V2 receptor antagonism in patients with liver cirrhosis

#### Rationale

V2 receptor antagonism may be particularly beneficial in the treatment of patients with advanced liver cirrhosis and ascites. Blockade of the V2 receptor will induce an effective aquaresis, as well as blocking effects have also been seen in clinical studies, where conivaptan had a good side-effect profile in healthy volunteers [49].

<table>
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<th>Table 2</th>
<th>Published clinical studies of V2 receptor antagonists relevant to liver disease</th>
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<td>Reference</td>
<td>Year</td>
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</table>
| [47] | 1995 | OPC-31260 | 3, 5, 30, 100, 200 mg/kg | Healthy, well hydrated men | 6 | Increased urine volume dose dependently  
Maximum dose (200 mg) increased plasma sodium  
Increased plasma vasopressin |
| [57] | 1998 | OPC-31260 | 30 mg/kg, single dose | Cirrhotics with ascites and peripheral oedema vs healthy subjects | 14 | Increased urinary excretion  
Lowered urinary osmolality  
Aquaretic responses 50% of those of controls |
| [56] | 1999 | VPA-985 | 50,100 mg BD | Cirrhotics with hyponatraemia (\(\leq 132 \text{ mmol/l}\)) | 60 | At 100 mg dose:  
Lowered urine osmolality  
Increased serum sodium  
Decreased body weight |
| [51] | 2001 | VPA-985 | 50, 100 mg BD | Hyponatraemic cirrhotics with ascites and SIADH patients | 11 | Lowered urine osmolality  
Increased serum sodium  
Increased urine volume |
| [44] | 2002 | VPA-985 | 25, 50, 100, 200, 300 mg | Cirrhotics with ascites | 25 | Increased free water clearance  
Increased serum sodium |
| [52] | 2003 | VPA-985 | 25, 125, 250 mg | Cirrhotics with ascites; patients with CHF or SIADH | 44 | Increased free water clearance  
Increased serum sodium |
| Forearm blood flow study | [17] | 1995 | OPC-31260 | Healthy subjects | 8 | Blocked vasopressin-induced vasodilatation but had no effect on nitroglycerine-induced vasodilatation |
the potential for \(V_2\)-mediated vasodilatation. This aquareesis, in combination with a diuresis, may provide a potential therapy for patients with resistant ascites. Moreover, \(V_2\) receptor antagonism increases the plasma vasopressin concentration \([44,51,52]\), which may cause unopposed hyperstimulation of the vasoconstrictor \(V_1\) receptors, especially given the high plasma vasopressin concentrations seen in cirrhosis \([22]\). Taken together, these effects present a particularly attractive theoretical haemodynamic and renal profile of action in these patients. Indeed, given the potential hyperstimulation of the \(V_1\) receptor, it is tempting to speculate that \(V_2\) receptor antagonists may have additional secondary preventative benefits in patients with cirrhosis through a reduction in portal pressure and a decreased risk of variceal bleeding.

**Pharmacological agents**

OPC-31260 was the first non-peptidic \(V_2\) receptor antagonist to be developed, and was introduced in 1992 \([4]\). Since then, two more compounds have become available: VPA-985 and SR121463A. In comparison with OPC-31260, they exhibit a higher affinity and selectivity for \(V_2\) receptors, thereby suggesting enhanced efficacy \([7]\).

**Animal studies**

Three published animal studies have examined the effects of \(V_2\) receptor antagonists in the rodent carbon tetrachloride model of liver cirrhosis. In all studies, \(V_2\) receptor antagonism resulted in a significant increase in urine volume and aquareisis \([3,53–55]\), without significant systemic haemodynamic effects. One study suggested that the aquaretic effect was short lived (2 days) and that tolerance to \(V_2\) receptor antagonism may develop \([54,55]\).

**Early clinical experience**

Clinical studies have mirrored these animal studies. Five trials have been performed in patients with cirrhosis, with all but one utilizing VPA-985 (Table 2) \([44,47,51,52,56]\). In the earliest trial, eight patients with biopsy-proven cirrhosis and ascites and six healthy subjects were given OPC-31260 as a single dose \([57]\). Consistent with the animal studies, this led to an increased urine volume and decreased urine osmolality. However, the aquaretic response was 50\% lower in patients with cirrhosis. Despite this apparent reduced efficacy in patients with cirrhosis, \(V_2\) receptor antagonism can still achieve dramatic effects, as exemplified by one patient who produced 16 litres of urine after administration of a single 300 mg dose of VPA-985 \([44]\).

In the largest single trial, 60 patients with cirrhosis and hyponatraemia \((\leq 132\ mmol/l)\) were given VPA-985 at either 50 mg or 100 mg in a placebo-controlled trial \([56]\). At the 100 mg dose, VPA-985 reduced urine osmolality, increased serum sodium and decreased body weight, without inducing any adverse effects. The North American VPA-985 study group examined the combined clinical experience of VPA-985 in patients with cirrhosis, heart failure or SIADH \([52]\). They confirmed that it was a safe agent in correcting conditions associated with water retention and hyponatraemia.

**Potential adverse effects**

Patients with advanced cirrhosis often have a precarious haemodynamic state, with low systemic blood pressure and renal dysfunction. Vasopressin antagonists may precipitate or exacerbate these problems by further reducing plasma volume. Moreover, too rapid an increase in the serum sodium concentration can precipitate central pontine myelinosis in patients with marked hyponatraemia. The incidence of these phenomena with the use of vasopressin antagonists is unknown.

The effects of blocking the vasopressin system on the coagulation cascade are poorly characterized. The \(V_2\) receptor agonist desmopressin increases plasma concentrations of Factor VIII, von Willebrand factor and tissue plasminogen activator \([58,59]\), an effect that is blocked by \(V_2\) receptor antagonism \([60]\). It is unclear whether the vasopressin system has a physiological role in the regulation of endogenous haemostasis or fibrinolysis, but there is a theoretical concern that vasopressin receptor antagonism may have important effects, and warrants surveillance and further investigation.

**CONCLUSION**

Vasopressin undoubtedly plays an important role in the pathophysiology of liver cirrhosis. It has significant effects on the regional regulation of vascular tone and blood pressure, and overstimulation of the \(V_2\) receptor leads to water retention and its sequelae.

The development of \(V_2\) receptor antagonists has provided a novel and promising therapeutic approach to the treatment of impaired water handling in cirrhosis. Clinical trials in patients with liver cirrhosis have produced the expected benefits of aquareesis and correction of hyponatraemia. Whether these agents prove to be superior to standard diuretic therapy or have secondary preventative benefits remains to be established in large-scale clinical trials of patients with cirrhosis.

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