The effects of vasopressin and its analogues on the liver and its disorders in the critically ill
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Purpose of review
Vasopressin and terlipressin, a long-acting V1a analogue, are increasingly used in intensive care. The main clinical indications are the treatment of patients with septic shock and of patients with cirrhosis, who develop variceal bleeding, the hepatorenal syndrome or both. In this review, we summarize the effects of these drugs on splanchnic hemodynamics and organ function.

Recent findings
A recent systematic meta-analysis of randomized trials suggests that terlipressin may improve renal function in hepatorenal syndrome and thereby reduce mortality by 34\%.

Furthermore, a recent study reported that association of terlipressin and albumin was more effective than terlipressin alone. In patients with variceal bleeding, the bleeding control is significantly improved by early administration of terlipressin. The place of vasopressin in the treatment of patients with septic shock is still discussed, but compared with norepinephrine, vasopressin showed at least an equal efficacy.

Summary

The use of vasopressin and its synthetic analogues has shown beneficial effects in the management of patients with cirrhosis, especially in the context of variceal bleeding, the hepatorenal syndrome or both. In both cases, the use of terlipressin improved survival. Therefore, in these clinical indications, terlipressin is a part of recommendations. The role of vasopressin in patients with septic shock remains to be precisely evaluated.

Keywords

cirrhosis, hepatorenal syndrome, septic shock, splanchnic hemodynamics, terlipressin, variceal bleeding, vasopressin

Introduction

Vasopressin and terlipressin, a long-acting V1a analogue, are increasingly used in intensive care. The main clinical indications are the treatment of patients with septic shock, and of patients with cirrhosis, who develop variceal bleeding, the hepatorenal syndrome (HRS) or both. In the following review, we summarize the effects of these drugs on splanchnic hemodynamics and organ function. Whenever possible, we only focus on clinical available data. Otherwise, experimental data are reported.

Physiopathology of V1a agonists in cirrhosis

The accumulation of fibrosis in liver (architectural changes) and the increased vascular tone in the intrahepatic microvascular bed (sinusoidal), which characterizes cirrhosis, lead to an increase in intrahepatic resistance to blood flow (high intrahepatic resistance). Intrahepatic vascular tone depends on perisinusoidal stellate cells (myofibroblasts), which are influenced by endogenous vasoconstrictors (i.e., norepinephrine, endothelin-1, angiotensin II, leukotrienes and thromboxane A\textsubscript{2}) and vasodilators (i.e., nitric oxide). For example, in cirrhosis, the increase in intrahepatic vascular resistance results from deficient intrahepatic nitric oxide production associated with high endothelin levels [1\*]. Thus, the increased vascular resistance to sinusoidal blood flow is the primary mechanism that increases portal pressure. Portal hypertension (portal pressure > 8 mmHg) leads to the development of collateral venous circulation, which causes a hyperdynamic circulatory state characterized by intense splanchnic and systemic arterial vasodilation. Splanchnic arterial vasodilation results from an excessive release of endogenous vasodilators such as nitric oxide and leads to increased portal blood flow, which in turn further aggravates portal hypertension. Finally, decreased systemic vascular resistance (systemic vasodilatation) is largely the result of the decrease in splanchnic arterial resistance (splanchnic vasodilatation). Moreover, cirrhosis is characterized by intrahepatic vascular hyperreactivity and systemic vascular hyporeactivity to various vasoconstrictors.

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Hemodynamic effects of vasopressin and terlipressin in cirrhosis

Several studies performed in portal hypertensive rats reported the following beneficial effects of vasopressin due to a powerful arterial splanchnic vasoconstriction: reduction of portal pressure, and thereby portosystemic collateral blood flow in combination with a decrease in cardiac index (CI) due to increased systemic vascular resistances and improvement of vascular reactivity [3]. The in-situ perfusion experiments suggested that vasopressin exerts a direct vasoconstrictive effect on the collateral vascular bed in extra and intrahepatic models of portal hypertension [4]. In cirrhotic patients without variceal bleeding, vasopressin has been shown to be active as well by decreasing portocaval venous pressure gradient (average fall of 25–50%), aygos blood flow (a reflect of collateral circulation), variceal blood flow and intravariceal pressure [5–7]. Moreover, in the same cirrhotic patients, vasopressin increased intrahepatic vascular resistance and decreased hepatic blood flow (~30%). However, the efficacy of vasopressin seems to be less pronounced in cirrhotic patients during severe variceal bleeding with hemorrhagic shock, as showed by experimental and clinical studies [8,9]. Terlipressin, a long-lasting synthetic vasopressin analogue, is slowly cleaved to vasopressin, has longer hemodynamic effects and less adverse effects than vasopressin [10]. Terlipressin and vasopressin have similar splanchnic and systemic hemodynamic effects in rats [11–14] and in cirrhotic patients [15].

Although terlipressin was reported to have powerful splanchnic vasoconstrictive effects, the intrahepatic hemodynamic effects may be different. Indeed, compared with vasopressin, terlipressin was reported to decrease intrahepatic vascular resistance due to dilution of hepatic sinusoids and was associated with increased arterial hepatic blood flow [16].

Variceal bleeding

The risk of variceal hemorrhage in untreated patients with cirrhosis and varices ranges between 8 and 35% at 2 years from cirrhosis diagnosis and, despite recent progress, variceal bleeding still carries a mortality around 15% in developed countries versus 50% in natural history.

In clinical practice, vasopressin is frequently associated with severe adverse effects (ischemia and arterial hypertension), so its use is recommended with nitrates in USA where no other vasoactive drug is marketed; in fact, nonapproved drugs are used. In other settings, terlipressin is recommended in cirrhotic patients, but terlipressin may still induce ischemic complications, although less severe, and is, therefore, contraindicated in patients with cardiovascular disease [17,18]. Terlipressin was found to be superior to placebo, and as effective as vasopressin, in the control of acute variceal bleeding, in term of survival, failure of initial hemostasis and blood transfusion requirements [19,20].

In variceal bleeding, administration of terlipressin [2 mg intravenous (i.v.) bolus each 6 h] is recommended for 2–5 days. The vasoactive treatment is always associated with endoscopic treatment and antibiotherapy. The dosage of terlipressin can be reduced on the second or third day if hemostasis is obtained. Under terlipressin administration, variceal bleeding is controlled in 70–80% of patients at 48 h, and the rebleeding is prevented in 67% of the patients at the fifth day. Moreover, the death rate is significantly reduced by early administration of terlipressin in patients with severe cirrhosis [20,21**,22,23].

Hepatorenal syndrome

HRS is a rapidly progressive and severe kidney injury due to severe vasoconstriction of the renal circulation that causes a marked reduction in renal blood flow and glomerular filtration rate. HRS is associated with high mortality. The renal vasoconstriction is due to the activation of vasoconstrictor systems (e.g., renin–angiotensin system) in compensation of reduced effective systemic arterial blood volume [24**].

As splanchnic and systemic vasodilatation play a major role for the development of HRS, administration of a powerful splanchnic vasoconstrictor such as terlipressin improves renal blood flow and increases glomerular filtration [25]. Several studies have assessed the efficacy of terlipressin and unanimously demonstrate that the increase in splanchnic arterial resistances by terlipressin, which acts through V1 vasopressin receptors, may improve HRS. A recent randomized controlled trial [26*], assessing terlipressin versus placebo, confirmed the findings of previous uncontrolled and small controlled pilot studies, suggesting improvement in renal function in HRS type 1 with terlipressin. Moreover, recent systematic reviews [18,27] of randomized trials suggest that terlipressin may improve renal function in HRS and reduce mortality by 34%. Finally, a recent study [24**]
reported that terlipressin combined with albumin was more effective than albumin alone.

Thus, terlipressin, combined with albumin, produces a complete reversal of HRS in 50–80% of individuals with improvement in survival [18]. Recurrence of HRS after terlipressin withdrawal may occur in 5–15% of individuals, but further treatment is usually effective [26**].

**V1a agonists in septic shock**

V1 agonists are thought to jeopardize splanchnic hemodynamics due to their potent vasoconstrictor effects. However, the regional vascular effects of vasopressin also largely depend on the experimental model and the species. More than 30 years ago, Schmid et al. [28] assessed the effect of incremental doses of vasopressin on mesenteric, renal and iliac blood flows in dogs. Vasopressin decreased blood flow in all three vascular beds; however, mesenteric and renal blood flows, expressed as percentage of cardiac output (CO), significantly increased at the expense of the iliac vascular bed, suggesting a redistribution of blood flow toward the splanchnic organs. Conversely, in rabbit, vasopressin had a vasoconstrictor effect on renal artery but not on the mesenteric artery [29].

**Role of fluid resuscitation**

Recently, our group reported in nonfluid-resuscitated endotoxic rats that infusion of vasopressin analogue terlipressin dramatically decreased splanchnic blood flow. Conversely, in fluid-challenged endotoxic rats, both splanchnic blood flow and ileal microcirculation, assessed by laser Doppler technique, were well maintained [30]. Indeed, whenever the experimental design led to a hypodynamic state, infusing a V1 agonist induced detrimental macro or microcirculatory effects in the splanchnic bed [31,32].

Detrimental effects of vasopressin in hypodynamic or normodynamic state were also reported by Hiltebrand et al. [33] in normotensive fecal peritonitis in pigs. Vasopressin significantly decreased superior mesenteric blood flow, which was associated with impaired markers of microcirculation. A recent study by the same group [34] reported in the same experimental model that low-dose (0.06 U/kg/h) vasopressin also significantly decreased portal venous flow, whereas hepatic artery blood flow remained unaltered. Both studies used models characterized by a hypodynamic circulation, that is, hypotension and depressed CO, which are thus in sharp contrast with the results of the studies in which V1a agonists were assessed in hyperdynamic models that are characterized by a sustained increase in blood flow [32,35–37]. In fact, Sun et al. [36] assessed the systemic and splanchnic hemodynamic effects of vasopressin versus norepinephrine versus the combination of both drugs during ovine fecal peritonitis, in which a hyperdynamic circulation was maintained due to aggressive fluid resuscitation. Both drugs significantly increased mesenteric blood flow, but vasopressin alone allowed maintaining mesenteric blood flow in the late phase of septic shock. Compared with control or norepinephrine alone, vasopressin alone or in combination with norepinephrine limited the increase in arterial lactate levels and the gastric to arterial pCO₂ gap, attenuated tissue injury and prolonged survival [36]. The crucial role of the adequate fluid challenge leading to hypodynamic state was further confirmed by others. In a first study, Martikainen et al. [31] assessed the effects of vasopressin versus norepinephrine in a hypodynamic endotoxic pig model. Vasopressin reversed hypotension but decreased systemic and gut blood flow, induced hyperlactatemia and signs of visceral dysxia such as visceral to arterial pCO₂ gaps, and jejunal luminal lactate release. In a subsequent experiment, dobutamine, added to vasopressin to induce a hypodynamic circulation, prevented the deleterious effects of vasopressin reported in their previous series [35]. We reported the effects of low-dose terlipressin targeted to maintain mean arterial pressure during long-term, hyperdynamic, volume-resuscitated porcine endotoxemia. Terlipressin increased mean arterial pressure and decreased CO. However, terlipressin restored the hepatic artery buffer response, which led to an increase in hepatic artery flow, ultimately resulting in well maintained liver O₂ delivery and uptake as well as all other variables of regional metabolism and organ function. Clearly, infusing terlipressin was associated with pronounced hyperlactatemia, which, however, did not originate from the splanchnic area, and markedly attenuated the hepatosplanchnic venous acidosis [37]. Finally, the two most recent experimental studies did not report any harmful effects of vasopressin on splanchnic hemodynamics. In their hypodynamic model of rabbit endotoxemia, Kopel et al. [38*] reported that low-dose vasopressin (<100 ng, i.v. bolus) altered neither mesenteric endoxemia (Doppler ultrasound probes) nor liver microcirculatory blood flow (laser Doppler flowmetry). Our group compared the effect of vasopressin and norepinephrine during long-term, resuscitated porcine fecal peritonitis-induced septic shock. Vasopressin not only limited the rate of endogenous glucose production but also increased the rate of the direct, aerobic oxidation, which coincided with lower arterial lactate concentrations. In addition, vasopressin attenuated the portal and hepatic venous acidosis and blunted the otherwise significant rise in serum transaminase activities and bilirubin [39**].

**Role of vasopressin dose**

Apart from the role of fluid challenge, both the infusion rate and the timing of vasopressin infusion also assume major importance. Malay et al. [40] reported the effects of incremental doses on global and regional circulations in
fluid-resuscitated endotoxic pigs. Low doses of vasopressin raised arterial pressure without detrimental effect on mesenteric blood flows, whereas higher doses induced ischemia in the mesenteric and renal circulations. Knotzer et al. [41,42] reported the effects of an incremental vasopressin infusion both in healthy [41] and endotoxic pigs [42]. The main result of these two studies was that incremental doses of vasopressin threatened the splanchic circulation as suggested by the fall in jejunal mucosal microvascular (μ)PO2 in nonendotoxic pigs. Strikingly, vasopressin had no further detrimental effect on mucosal oxygenation beyond that of endotoxin per se in the endotoxic animals.

Clinical studies
Most of the published studies [43–46] used tonometry to assess the effects of V1a agonists on splanchic hemodynamics, and the results are conflicting.

A short-term study [47] in 12 patients with septic shock reported that a switch from norepinephrine (0.18–1.1 μg/kg/min) to high dose of vasopressin (0.06–1.8 μU/min) doubled the gastric mucosal–arterial PCO2 gradient (from 18 ± 27 to 37 ± 27 mmHg). Splanchnic blood flow non-significantly decreased, but the fractional splanchnic blood flow (expressed as percentage of CO) increased significantly from 11 ± 8 to 26 ± 17%. Interestingly, Dünset et al. [43] reported an increase in bilirubin levels, suggesting detrimental effects on liver function.

Pragmatically, the published trials [44–46,48–52] assessing V1a agonist in patients with septic shock did not report mesenteric ischemia, and in the largest trial [53**], the incidence of mesenteric ischemia was similar (2.3 versus 3.4%) for vasopressin and the control arm treated with norepinephrine. Of note, patients with mesenteric ischemia were excluded. However, concerns regarding potential splanchnic ischemic side effects of V1a are still not ruled out. In eight patients with vasodilatory shock, continuous infusion of incremental doses of vasopressin was reported to decrease ileal microcirculatory flow assessed by laser Doppler and tonometry [54*]. However, it should be mentioned that the mean CI was low and that four patients were treated with milrinone and intraaortic balloon pump. In patients with septic shock, continuous terlipressin versus vasopressin or norepinephrine were assessed in a randomized, controlled pilot study. Compared with terlipressin, vasopressin decreased the indocyanine green-dye plasma disappearance rate, a mirror of hepatic flow and excretory function, whereas gastric tonometry measurements remained unaltered. Interestingly, terlipressin but not vasopressin or norepinephrine significantly limited the increase in serum bilirubin levels [55**]. As increased bilirubin levels were also reported by Dünset et al. [44], a putative vasopressin-induced depression of hepatic excretory function warrants further exploration. It should be noted that no clear data are available in cirrhotic patients.

Conclusion
V1a agonists are increasingly used in intensive care. The use of these drugs has shown beneficial effects in the management of patients with cirrhosis, especially in the treatment of variceal bleeding and the HRS. As terlipressin improved survival in both cases, its use is recommended under these clinical indications, especially in HRS. The beneficial effect of vasopressin in patients with septic shock is less clear. Addition of vasopressin to norepinephrine did not show harmful effect in the largest reported clinical trial (Vasopressin And Septic Shock Trial), and thus vasopressin may represent a valuable alternative to norepinephrine. The effects of terlipressin were assessed in smaller pilot studies, and thus it is too early to state an opinion on its putative superiority as compared with norepinephrine or vasopressin. In our opinion, in future clinical trials, one of the key points is to select patients with septic shock who have high CO.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 179).

**Gastrointestinal system**


22. An excellent synthetic review with the most advances in diagnosis, pathophysiology and treatment of variceal bleeding.


This study reported that association of terlipressin and albumin is more effective than albumin alone in the management of HRS.


This first international randomized control study reported the significant improvement in renal function in cirrhotic patients with HRS treated by terlipressin, and showed that improvement in renal function improves overall survival in patients with HRS.


