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REVIEW ARTICLE

Vasopressin and terlipressin: pharmacology and its clinical relevance

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Summary

Vasopressin and its analogue, terlipressin, are potent vasopressors that may be useful therapeutic agents in the treatment of cardiac arrest, septic and catecholamine-resistant shock and oesophageal variceal haemorrhage. The aim of this article is to review the physiology and pharmacology of vasopressin and summarise its efficacy and safety in clinical trials and its subsequent therapeutic use. Recent studies indicate that the use of vasopressin during cardiopulmonary resuscitation may improve the survival of patients with asystolic cardiac arrest. Vasopressin deficiency can contribute to refractory shock states associated with sepsis, cardiogenic shock and cardiac arrest. Low doses of vasopressin and terlipressin can restore vasomotor tone in conditions that are resistant to catecholamines, with preservation of renal blood flow and urine output. They are also useful in reducing bleeding and mortality associated with oesophageal variceal haemorrhage. The long-term outcome of the use of these drugs is not known.

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Clinical experience of vasopressin as an alternative to epinephrine for the vasopressor therapy in cardiopulmonary resuscitation is limited [1,2] although it is now included in the American Heart Association 2000 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care for the treatment of unstable ventricular tachycardia and ventricular fibrillation [3]. It is also used to treat diabetes insipidus and oesophageal variceal bleeding [4,5].

The aim of this article is to summarise the relevant physiology and pharmacology of vasopressin and its analogues, and review their therapeutic applications and safety in patients with refractory circulatory collapse or cardiac arrest.

Physiology of vasopressin

Vasopressin, a nona-peptide, is synthesised as a large prohormone in the paraventricular and supraoptic nuclei of the hypothalamus. The hormone which is bound to neurohypophysin (an axonal carrier protein) is transported along the supraoptic-hypophyseal tract to the axonal terminals of the magnocellular neurones located in the *pars nervosa* of the posterior pituitary gland. Ten to 20% of the total vasopressin pool within the posterior pituitary is rapidly released initially, and subsequently secreted at a greatly reduced rate in response to appropriate stimuli. The entire process of vasopressin synthesis, transport and storage in the posterior pituitary takes 1–2 h [6]. The most potent stimuli to vasopressin release are increased plasma osmolality and severe hypovolaemia. Central nervous input mediated by pain, nausea, hypoxia, pharyngeal stimuli and endogenous and exogenous chemicals also increase vasopressin release. Hyperosmolality, sensed by central and peripheral osmoreceptors, is a potent stimulus for the release of vasopressin. The central osmoreceptors (subfornical organ nuclei, *organum vasculosum lamina terminalis*) located

outside the blood–brain barrier detect changes in systemic osmolality. Peripheral osmoreceptors, located in the hepatic portal veins, enable early detection of the osmolality of ingested food and fluids. Afferent impulses ascend via the vagus nerve to the *nucleus tractus solitarius, area postrema* and *ventrolateral medulla* and then project to the paraventricular nuclei and supraoptic nuclei (located within the blood–brain barrier). The final common pathway of vasopressin release involves its synthesis in the paraventricular nuclei (magnocellular neurone cell bodies), and transport via the supraoptic–hypophyseal tract to the *pass nervosa*. Plasma hypertonicity depolarises the magnocellular neurones of the hypothalamus causing more vasopressin release.

Volume and pressure stimuli modify vasopressin release. Hypovolaemia causes an exponential increase in vasopressin levels and this is mediated by hypotension and decreased intravascular volume. It increases the threshold for vasopressin release by shifting the osmolality–vasopressin response curve upwards and to the left without changing its slope (sensitivity). Higher plasma vasopressin levels are required to maintain normal osmolality in hypovolaemic states [7]. Afferent vagal impulses from the left atrial, aortic arch and carotid sinus stretch receptors tonically inhibit vasopressin secretion. Atrial receptors respond to increases in blood volume whereas the receptors in aortic arch and carotic sinuses respond to increases in arterial blood pressure. Diminished arterial baroreceptor activity increases vasopressin release during severe hypotension. A decrease in central venous pressure causes an increase in plasma norepinephrine and renin concentrations, whereas the plasma vasopressin concentration does not increase until mean arterial pressure decreases [8]. Volume expansion and large increases in blood pressure transiently inhibit vasopressin release, mediated by the atrial stretch receptors.

Acetylcholine (via nicotinic receptors), histamine, dopamine, prostaglandins, angiotensin and other catecholamines directly stimulate vasopressin release. High $PaCO_2$ stimulate carotid body chemoreceptors and thus increase vasopressin levels. Opioids, γ-aminobutyric acid and atrial natriuretic peptide inhibit vasopressin via α_1-adrenoreceptors whereas the α_2-adrenoreceptors and β-adrenergic receptors inhibit vasopressin and oxytocin release [9].

The normal fasting vasopressin concentration in humans is < 4 pg.ml^{-1}. Small increases in plasma osmolality are rapidly sensed, and the vasopressin concentration increases to 10 pg.ml^{-1}. Vasopressin levels ≥ 20 pg.ml^{-1} cause maximal increase in urine osmolality. The half-life of vasopressin is 10–35 min. It is rapidly metabolised by liver and kidney vasopressinases [10].

Vasopressin receptors

Vasopressin receptors are G-protein coupled receptors with seven transmembrane spanning domains. The distribution and density of vasopressin receptors account for the potentially beneficial pharmacological effects [11].

There are three subtypes of vasopressin receptors. V_1 vascular receptors (formerly known as V_{1a} receptors) mediate vasoconstriction and are located on vascular smooth muscle. V_1 receptors are found in the kidney, myometrium, bladder, hepatocytes, platelets, adipocytes and spleen. V_1 mediated vasoconstriction is mediated by Gq protein coupled activation of phospholipase C that releases Ca^{++} from intracellular stores via inositol triphosphate and diacylglycerol.

V_2 renal receptors are Gs protein linked receptors on the basolateral membrane of distal tubal and collecting ducts that activate adenylyl cyclase to increase cyclic adenosine monophosphate (AMP). This mobilises aquaporin channels, which are inserted into the apical membrane of the renal collecting duct cells and endothelial cells. The V_2 renal receptors are therefore responsible for the antidiuretic effects of vasopressin.

The V_3 pituitary (formerly known as V_{1b}) receptors activates Gq protein and release intracellular Ca^{++} after activation of phospholipase C and the phospho-inositol cascade. V_3 receptor activation in the pituitary gland stimulates adrenocorticohormone (ACTH) secretion from the anterior pituitary gland. The V_3 receptors are responsible for the actions of vasopressin on the central nervous system, where they act as neurotransmitter or a modulator controlling memory, blood pressure, body temperature and release of pituitary hormones [12].

Human vascular endothelial cells express oxytocin receptors [13]. Low concentrations of vasopressin activate oxytocin receptors located in endothelial cells of human umbilical vein, aorta and pulmonary artery, causing vasodilatation, mediated by stimulation of the nitric oxide pathway on endothelial cells [13]. High concentrations of vasopressin activate phospholipase A_2 and cyclic AMP production, mediated by coupling to Gi and Gs proteins, respectively.

Physiological effects of vasopressin

Vasopressin is a direct systemic vasoconstrictor (mediated by V_1 receptors). It is important for osmoregulation and maintenance of normovolaemia (mediated by renal V_2 receptors). It also maintains haemostasis, plays a role in temperature regulation, memory and sleep and promotes ACTH release. Under normal physiological conditions, the main physiological role of vasopressin is the regulation of water balance. It is released from the posterior pituitary

in response to increased plasma osmolality or reduced plasma volume.

Under normal conditions and at normal physiological concentrations, vasopressin does not have a major role in the vascular regulation of blood pressure. Plasma vasopressin concentrations of about 50 $pg.ml^{-1}$ must be attained before a significant increase in mean arterial blood pressure is achieved in humans [14]. However, during hypotension caused by hypovolaemia, plasma vasopressin levels increase and this is important for preserving perfusion pressure [15]. Vasopressin is a weak vasopressor in animals with an intact autonomic nervous system. It causes a leftward shift of the heart rate-arterial pressure baroreflex curve by acting on V_1 receptors in the brain [16]. It is a potent vasoconstrictor in skin, skeletal muscle, fat, pancreas and thyroid gland [17]. It causes less vasoconstriction in coronary and cerebral circulations compared with the catecholamines [18]. Vasopressin also augments the sensitivity of the vasculature to norepinephrine [19].

Vasopressin blocks potassium sensitive adenosine triphosphate (K-ATP) channels in a dose-dependent manner. Activation of K-ATP channels causes vasodilation by decreasing Ca^{++} channels [20]. It also vasoconstricts the mesenteric circulation at physiological concentrations (< 10 $pg.ml^{-1}$), mediated by the V_1 receptor. This effect may be important in restoring vascular tone in patients with septic shock.

Vasorelaxation, produced by vasopressin at low concentrations, is endothelium dependent and mediated by nitric oxide. The arteries of the Circle of Willis vasodilate to a greater extent compared to other intracranial and extracranial arteries. Vasopressin induced vasodilation is mediated by endothelial oxytocin receptors which mobilise intracellular calcium and release nitric oxide [20]. It causes pulmonary vasodilatation mediated by release of endothelium – derived nitric oxide at plasma concentrations < 300 $\mu g.ml^{-1}$. However, pulmonary vascular resistance increases at very high plasma concentrations of vasopressin which exceed 500 $\mu g.ml^{-1}$.

Renal effects

Vasopressin regulates urine osmolality by increasing the permeability of the luminal membranes of the principal cells of the collecting ducts of the kidney. V_2 receptors, located at the baso-lateral membrane of the principal cells, are activated and increase intracellular cyclic AMP which via protein kinase activation, cause aquaporin to fuse with the luminal membrane. This concentrates the urine. Vasopressin also enhances the concentration of the urine by other mechanisms; including increasing the medullary concentration gradient by activating a distinct urea transporter and decreasing the inner medullary blood flow without altering the cortical blood flow [21].

Vasopressin stimulates the release of ACTH via the V_3 receptor. Pharmacologic doses of vasopressin induce a prompt increase in plasma cortisol levels in men, mediated by nitric oxide and cyclic guanosine monophosphate (GMP) via the V_3 receptor [22].

Vasopressin causes platelet aggregation by enhancing the release of Von Willebrand Factor and Factor $VIII_c$ from the endothelial cells [23]. In the brain vasopressin appears to act as a neurotransmitter and is involved in the central control of circadian rhythm [24], cardiovascular regulation, thermoregulation and regulation of ACTH release [25].

Pharmacology of vasopressin and terlipressin

Exogenous vasopressin (8-arginine vasopressin) [Fig. 1] is presented as a sterile aqueous solution of synthetic vasopressin for intravenous, intramuscular and subcutaneous administration. It is not protein bound and has a volume of distribution of 140 $ml.kg^{-1}$. The plasma half-life of vasopressin is 24 min. It is cleared by renal elimination (65%) and metabolism (35%) by tissue peptidases [2].

Terlipressin (triglycyl – lysine vasopressin) [Fig. 2] became popular in the early 1990s because it has a

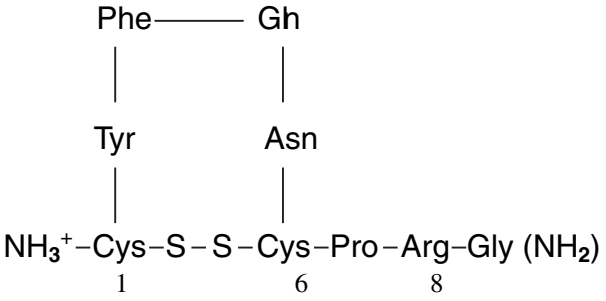

Figure 1 Arginine vasopressin. Cys = Cysteine, Phe = Phenylalanine, Tyr = Tyrosine, Gln = Glutamine, Asn = Asparagine, Pro = Proline, Arg = Arginine, Gly = Glycine.

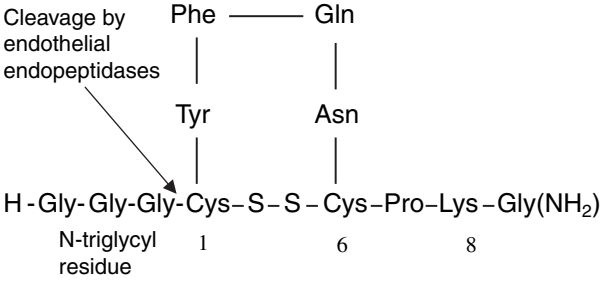

Figure 2 Lysine (Lys) is substituted for Arginine at position 8 of the vasopressin molecule. The N-triglycyl residue is cleaved by endothelial peptidases, releasing the active lysine-vasopressin.

prolonged duration of action. It is a prodrug and is converted to the lysine vasopressin in the circulation after the N-triglycyl residue is cleaved by endothelial peptidases. This results in a 'slow release' of the vasoactive lysine vasopressin [26]. The effect half–life of terlipressin is 6 h. It causes a prolonged reduction of portal venous pressure (mean 103 min) [27]. The elimination half-life of terlipressin is 50 min [28].

Vasopressin deficiency can contribute to hypotension observed in patients with catecholamine resistant septic shock, postcardiotomy shock and cardiac arrest. Laboratory studies and clinical reports suggest that administration of vasopressin infusions to yield plasma concentration of vasopressin 20–30 $pg.ml^{-1}$ produce a pressor response with minimal organ hypoperfusion [1,2]. The administration of low intravenous doses of vasopressin restores the vasomotor tone with minimal renal, mesenteric, pulmonary and cardiac ischaemia. However, routine clinical use of vasopressin should await randomised clinical trials to determine the effect of vasopressin on clinical outcomes such as organ failure, long-term outcomes and mortality.

Efficacy of vasopressin and its analogues in shock

Endogenous vasopressin is considered a stress hormone that is released in response to pain, surgery, syncope and shock [29]. Vasopressin concentrations are raised in patients who have cardiogenic shock following myocardial infarction, haemorrhage and sepsis [30–35]. Haemorrhage and septic shock cause biphasic changes in vasopressin concentrations. In early shock, high concentrations of vasopressin are produced to maintain organ perfusion. As the shock state progresses, plasma vasopressin concentrations decrease. In animal studies, hypotensive haemorrhage in dogs and monkeys increased plasma vasopressin concentrations to 100–1000 $pg.ml^{-1}$, which subsequently decreased to 29 $pg.ml^{-1}$. In humans plasma vasopressin concentration may increase to 22 $pg.ml^{-1}$ in early cardiogenic shock and then decrease to 3 $pg.ml^{-1}$ in late shock. The proposed mechanisms to explain the depletion of vasopressin include (a) depletion of neurohypophyseal stores of vasopressin in refractory shock caused by excessive baroreceptor firing (b) autonomic insufficiency and (c) elevated endogenous norepinephrine concentrations that have a central inhibitory effect on vasopressin release [30,31].

Septic shock is associated with vasopressin deficiency and a hypersensitivity to its exogenous administration. Vasodilatation combined with severe vascular hyporeactivity to catecholamine therapy may occur and these patients have a high cardiac output and low systemic resistance circulation. Although two-thirds of patients respond to corticosteroids (which restore adrenoceptor sensitivity and inhibit nitric oxide synthase) or methylene blue (which inhibits guanylate cyclase and nitric oxide synthase), non-responders often die from intractable hypotension within a day [35].

Landry *et al.* observed that patients with advanced septic shock had low mean (SD) plasma levels of vasopressin. 3.1 (0.4 $pg.ml^{-1}$) caused by impaired secretion [36]. Exogenous infusion of 0.01 $U.min^{-1}$ of vasopressin restored the vasopressin concentration to 27–34 $pg.ml^{-1}$. Septic shock patients have an increased sensitivity to low-dose vasopressin. In 10 patients who received vasopressin at 0.04 $U.min^{-1}$, plasma vasopressin concentration increased to 100 $pg.ml^{-1}$ and this was associated with an increased systolic blood pressure (92–146 mmHg), increased systemic vascular resistance (by 79%) and a decrease in cardiac output (by 12%). Plasma levels of vasopressin of 30 $pg.ml^{-1}$ were achieved when the infusion rate of vasopressin was reduced to 0.01 $U.min^{-1}$. Six patients maintained adequate perfusion pressures with vasopressin as the sole pressor. Discontinuation of vasopressin infusion caused a sudden decrease in arterial pressure.

In a randomised controlled trial involving 10 patients with vasodilatory shock following trauma, five patients receiving vasopressin at 0.04 $U.min^{-1}$ increased their systolic blood pressure (98–125 mmHg) via peripheral vasoconstriction (systemic vascular resistance 878–1190 $dynes.s.cm^{-5}$) and were completely weaned from catecholamines [37]. All patients in the vasopressin treatment group survived. The patients in the control group had no increase in blood pressure and two patients died from refractory hypotension within 24 h.

A prospective randomised controlled study in of 48 patients with catecholamine-resistant shock showed that a combined infusion of vasopressin (4 $U.h^{-1}$) and norepinephrine (> 2.26 $\mu g.kg^{-1}.min^{-1}$) was superior to an infusion of norepinephrine alone [38]. Mean arterial pressure, cardiac index and left ventricular stroke index were significantly higher in the vasopressin treated patients. The vasopressin treated patients had less tachyarrhythmias and gastrointestinal perfusion (as measured by gastric tonometry) was better preserved.

Vasopressin can be beneficial in the treatment of excessive vasodilation associated with cardiopulmonary bypass. In a prospective study of 145 cardiac surgical patients, 11 had postbypass vasodilation with hypotension associated with vasopressin deficiency. This syndrome is common in patients with low ejection fraction and those receiving angiotensin converting enzyme inhibitors. Vasopressin (0.1 $U.min^{-1}$) produced significant increases in mean arterial pressure and systemic vascular resistance

with significant reduction in norepinephrine infusion requirements [39]. The initial infusion was rapidly decreased to 0.01 $U.min^{-1}$. In patients on long-term angiotensin converting enzyme inhibitors, intra-operative hypotension associated with general anaesthesia may be refractory to treatment with norepinephrine, phenylephrine and ephedrine. In these patients terlipressin (1 mg) is an effective vasopressor if they are refractory to common adrenergic vasopressors [40].

In postcardiotomy shock resistant to catecholamine therapy, continuous vasopressin infusion can be useful. In a group of patients with vasodilatory hypotension after cardiopulmonary bypass that received left ventricular assist device, treatment with vasopressin (0.1 $U.min^{-1}$) produced significant increases in mean arterial pressure with reduced norepinephrine requirements. Plasma vasopressin levels of 150 pg $.ml^{-1}$ were achieved [41]. In a retrospective study of 41 postcardiotomy shock patients who received vasopressin, there were significant decreases in heart rate, cardiac arrhythmias, milrinone and norepinephrine requirements, serum markers of myocardial ischaemia (Troponin – I and creatinine kinase myocardial band [MB]) and a significant increase in left ventricular stroke work index, mean arterial pressure and systemic vascular resistance [42]. During the infusion 45% of postoperative new-onset tachyarrhythmias were converted into sinus rhythm.

Terlipressin (1–2 mg intravenously) is a useful vasopressin analogue that produces sustained increases in blood pressure in septic patients [35]. In a series of eight patients with septic shock who did not respond to corticosteroids and methylene blue, a significant increase in blood pressure that lasted for 5 h was achieved in all patients after a single bolus of terlipressin (1–2 mg), enabling reduction or cessation of norepinephrine administration in seven patients. Terlipressin may be an effective rescue therapeutic agent that can restore blood pressure in catecholamine resistant septic shock.

Role of vasopressin in cardiac arrest

The current international guidelines for cardiopulmonary resuscitation recommend epinephrine during cardiac resuscitation and consider vasopressin only as a secondary alternative because the clinical data on the efficacy of vasopressin is limited. Of the 1000 sudden deaths that occur each day in the United States, an estimated 20–40% result from asystolic cardiac arrest [43]. Plasma concentrations of vasopressin consistently increase in cardiogenic and hypovolaemic shock (22.7 (SD 2.2) $pg.ml^{-1}$) in contrast to the low (3.1 (SD 1) $pg.ml^{-1}$) concentrations in patients with septicaemic shock (with similar blood pressures) [44,45]. In cardiac arrest patients, endogenous vasopressin concentrations increase within the first 60 s. Mean vasopressin concentrations are significantly higher in patients who are successfully resuscitated (122 $pg.ml^{-1}$ vs. 88 $pg.ml^{-1}$ in unsuccessful cardiopulmonary resuscitation). During closed chest cardiac compression, the cardiac output is rarely greater than 30% of baseline cardiac output [46,47]. A coronary perfusion pressure greater than 20 mmHg is essential for successful resuscitation [48]. Vasopressin is theoretically an attractive alternative to epinephrine during cardiopulmonary resuscitation because it significantly improves total cerebral and left myocardial blood flow, and causes a sustained increase in mean arterial blood pressure compared with maximal doses of epinephrine [49].

Animal studies

In a pig model of ventricular fibrillation, a dose–response study of 3 vasopressin doses (0.2, 0.4 and 0.8 $U.kg^{-1}$ compared with 200 $\mu g.kg^{-1}$ epinephrine (maximal effective dose) showed that 0.8 $U.kg^{-1}$ vasopressin was the most effective drug for increasing coronary perfusion pressures and total cerebral blood flow. Vasopressin (8 $U.kg^{-1}$) maintained cerebral and myocardial blood flow with higher coronary perfusion pressures compared with epinephrine (200 $\mu g.kg^{-1}$) [50]. Coronary perfusion pressure during cardiopulmonary resuscitation increased from 10 (SD 2) mmHg to 70 (SD 5) and 47 (SD 6) mmHg at 90 s and 5 min after vasopressin treatment in the vasopressin treated group compared with 12 (SD 2), 36 (SD 5) and 18 (SD 2) mmHg in the epinephrine group. Total cerebral blood flow at 90 s and 5 min were 78 (SD 5) $ml.min^{-1}.100\ g^{-1}$ and 30 (SD 3) $ml.min^{-1}.100\ g^{-1}$ in the vasopressin group compared with 38 (SD 2) and 30 (SD 3) mmHg with epinephrine. After vasopressin treatment, left ventricular and total cerebral blood flow were 217% and 111% above baseline values, compared with 29% and 22% above baseline values achieved with epinephrine.

Further, vasopressin significantly improved cerebral oxygen delivery when compared with the maximum dose of epinephrine [51]. The increased cerebral blood flow lasted longer with vasopressin administration than after epinephrine (4 min vs. 1.5 min). More animals that received vasopressin could be resuscitated (8 out of 9 vs. 1 out of 9) compared with epinephrine [49]. In another animal study, after the administration of repeated doses of vasopressin compared with those of epinephrine, coronary pressures increased after each of the three vasopressin doses but only increased after the first of the three epinephrine injections. All the pigs receiving vasopressin survived whereas all those resuscitated with epinephrine died [52].

Simulation of a prolonged (22 min) advanced cardiac life support in pigs found that spontaneous circulation returned in all pigs that received vasopressin, whereas all those in the epinephrine and saline placebo group died. After 24 h the only neurological deficit of all pigs that received vasopressin was an unsteady gait from which the animals completely recovered within three days. Magnetic resonance studies showed that there was no cerebral oedema or cerebral infarction. This suggested that the pigs had full anatomical and physiological recovery from cardiac arrest [53].

Human Studies

In eight patients with refractory cardiac arrest, vasopressin increased arterial blood pressure and prompted a return of spontaneous circulation when routine cardiopulmonary resuscitation measures (external cardiac compressions, ventilation, defibrillation and epinephrine) had failed [54]. In a prospective randomised study of 40 patients who suffered out-of-hospital ventricular fibrillation, Lindner *et al.* reported that a significantly larger proportion of patients treated with vasopressin were resuscitated and survived 24 h compared with those treated with epinephrine [55]. Twelve out of 20 patients in the vasopressin group survived compared to four survivors in the epinephrine group.

Since the publication of the current advanced cardiac life support (ACLS) guidelines Stiell *et al.* reported a prospective study of 200 patients with 'in-hospital' cardiac arrest (pulseless electrical activity (48%), asystole (31%), ventricular tachycardia (3%) or ventricular fibrillation (18%) who were randomised to receive either vasopressin (40 units) or epinephrine (1 mg) as the initial medication. The times to treatment were 1.4–1.9 min from collapse to cardiopulmonary resuscitation and 1.21–1.3 min for cardiopulmonary resuscitation to advanced cardiac life support. No difference in the survival rate at 1 h (vasopressin 39%; epinephrine 35%) and at 30 days (vasopressin 13%; epinephrine 14%) was observed [56]. Vasopressin did not improve or worsen survival in cardiac arrest from pulseless electrical activity, asystole or refractory ventricular fibrillation when compared with epinephrine. Several differences in these two trials may explain the differences in the results. Vasopressin was administered much later (7.8–8.6 min from cardiopulmonary resuscitation) in Lindner's study, compared with 1.1–1.3 min in Stiell's study. Compared with epinephrine, vasopressin exerts a greater vasoconstriction in hypoxic and acidotic conditions [57] and consequently the rapid response and early treatment in Stiel's trial may explain the lack of difference observed between vasopressin and epinephrine.

A large prospective multicentre double-blind, randomised controlled clinical trial of patients with out-of hospital cardiac arrest in Austria, Germany, and Switzerland reported that patients with refractory cardiac arrest were three times more likely to survive when treated with vasopressin compared with the standard emergency treatment with epinephrine [58]. The patients who suffered an out-of hospital cardiac arrest were randomly assigned to receive either vasopressin (40 U) or epinephrine (1 mg), followed by additional treatment with epinephrine if needed. The primary end point was survival to hospital and the secondary end point was survival to hospital discharge. Of the 1186 patients in the study, 589 received vasopressin and 597 received epinephrine. The two treatment groups had similar clinical profiles. Among patients with asystolic cardiac arrest, 29.0% of the patients in the vasopressin group compared with 20.3% were admitted to hospital (odds ratio 0.6 [95% confidence limits (CI) 0.4–0.9]). The percentage of patients who survived to discharge was also higher in the vasopressin group (4.7% vs. 1.5%; odds ratio 0.3[95% CI 0.1–1.0]). Among the patients with ventricular fibrillation there was no difference between the two groups (46.2% of vasopressin group vs. 43% in the epinephrine group; odds ratio 0.9[95% CI 0.6–1.3]). Neither was there a difference among patients with pulseless electrical activity (33.7% vs. 30.5%; odds ratio 0.8[95% CI 0.5–1.6]). In addition, among the 732 patients in whom spontaneous circulation was not achieved with the initial injections, subsequent treatment with additional epinephrine led to a higher proportion of patients surviving to hospital admission and hospital discharge in the vasopressin group than in the epinephrine group (hospital admission: 25.6% vs. 16.4%; hospital discharge: 6.2% vs. 1.7%).

Efficacy in the management of bleeding oesophageal varices

Over the last 40 years it has been increasingly appreciated that a hyperdynamic circulation and increased portal venous inflow play major roles in the development of portal hypertension [59]. 'Posterior pituitary extract' was first administered to patients with bleeding oesophageal varices in the 1960s [60]. Additional studies using vasopressin, lysine vasopressin and pitressin were conducted from mid 1970s to the late 1980s. As vasopressin binds to the V_1 receptor of vascular smooth muscle cells, it vasoconstricts the mesenteric arterial circulation leading to decreased portal venous inflow and a subsequent reduction in portal pressure. Acute variceal bleeding is controlled in 29–71% of patients treated with vasopressin alone, and in 45–73% of cases when vasopressin is combined with nitroglycerin (which relaxes portal venous circulation enhancing reduction in portal venous pressure [4]. Vasopressin is typically used as an infusion of

0.4 to 1.0 $U.min^{-1}$ in combination with nitroglycerin 50 $\mu g.min^{-1}$ intravenously. Higher doses of vasopressin are associated with increased side-effects such as myocardial and gastrointestinal ischaemia. A recent meta-analysis showed that terlipressin reduced mortality (relative risk 0.66 [95% CI 0.49–0.88]), improved haemostasis (relative risk 0.63 [95% CI 0.45–0.89]) and decreased the number of emergency procedures required for rebleeding (relative risk 0.72 [95% CI 0.55–0.93]) [61]. A mortality rate of 36% (80 out of 220 patients) was found in the placebo control group and one would need to treat eight patients with terlipressin instead of placebo to prevent one death (NNT = 8). The study also showed that terlipressin when added to sclerotherapy leads to improved haemostasis (relative risk 0.75 [95% CI 0.58–0.96]) as well as to reduction in mortality (relative risk 0.74 [95% CI 0.53–1.04]). The advantages of terlipressin include the convenience of a bolus administration, decreased cardiotoxicity and its ability to control approximately 70% of variceal haemorrhages [62]. Terlipressin is the only pharmacological agent to reduce mortality in acute oesophageal bleeding compared to placebo [61].

Efficacy in the treatment of hepatorenal syndrome

Vasopressin analogues used in conjunction with albumin improve renal function in hepatorenal syndrome. In a clinical trial of 21 patients, treatment with terlipressin (0.5–2 mg over 4 h) and albumin was associated with a significant decrease in serum creatinine concentrations, increase in arterial pressure, and suppression of the renin-aldosterone system [26].

Adverse effects of vasopressin

Severe skin necrosis after extravasation of low dose vasopressin administered for catecholamine resistant septic shock has been reported and peripheral administration of low dose vasopressin infusions should be discouraged [63]. Because vasopressin activates V_2 receptors on endothelial cells causing a release of endothelial Von Willebrand factor, it enhances platelet aggregation and therefore may increase the risk of thrombosis [64]. Hyponatraemia, anaphylaxis, bronchospasm, urticaria and ischaemia of the gastrointestinal tract have been reported [48].

Conclusions

Vasopressin deficiency can contribute to refractory shock states associated with sepsis, cardiogenic shock and cardiac arrest. Low doses of vasopressin and terlipressin can restore vasomotor tone in conditions that can be resistant to catecholamines, with preservation of renal blood flow and urine output. They are also useful in reducing bleeding and mortality associated with oesophageal variceal haemorrhage. The long-term outcome of the use of these drugs is not known.

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