Commentary

Terlipressin or Europressin?

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Abstract

Use of terlipressin in septic shock relies on a series of European studies resulting in a better knowledge of this vasopressive agent. Additional studies demonstrate that this agent appears to have attractive properties when administered properly. In comparison to prior reports, continuous infusion of low-dose terlipressin seems superior when administered to septic animals. For the first time in humans, Morelli and colleagues compared this mode of administration with other vasopressors.

In the previous issue of *Critical Care*, a European group made a new contribution to the terlipressin literature [1]. For the first time, terlipressin, vasopressin, and norepinephrine were compared among patients with septic shock. Because vasopressin is not available in most European countries, terlipressin, a vasopressin analog, was used in patients with norepinephrine-resistant septic shock. Terlipressin is initially indicated in patients with hepatorenal syndrome and bleeding esophageal varices. In 2001, a German group showed its efficacy in endotoxemic sheep [2]. In 2002, a British group treated eight patients with norepinephrine-resistant septic shock by repeated bolus administration of terlipressin [3]. In 2004, studies from France, Spain, and Italy confirmed the feasibility of terlipressin in septic shock [4-6].

Vasopressin and its analogs act on three subtypes of receptors: V1, V2, and V3 [7]. V1 receptors are found on various cells, including vascular smooth muscle cells, causing vasoconstriction. V2 receptors are expressed by kidney-collecting duct cells and mediate water retention. V3 receptors are found on cells within the central nervous system and modulate corticotrophin secretion. In septic shock, treatment is aimed to stimulate V1 receptors, and the vascular selectivity (V1/V2) of terlipressin is 2.2/1.0 compared with 1.0/1.0 for vasopressin [8].

Initially, terlipressin was used as a substitute for vasopressin. The difference is their pharmacokinetics [7]. The half-life of terlipressin is 6 hours compared with 20 minutes for vasopressin. Because of the prolonged half-life of terlipressin, patients with septic shock received repeated boluses (1 mg) of the drug [3,4]. After intravenous injection, terlipressin works as a prodrug that slowly metabolizes to lysine-vasopressin and in this way provides prolonged biological effect. Nevertheless, a recent paper shows that terlipressin is not only a prodrug of vasopressin but also a strong vasoconstrictor *per se* [9]. With regard to vasopressin, terlipressin may by itself have certain specific properties.

Because of its strong vasopressive effects, excessive vasoconstriction and a decrease in cardiac index are associated with bolus injection of terlipressin [3-6]. It was therefore hypothesized that low-dose continuous infusion may reverse sepsis-related systemic arterial hypotension with reduced side effects. In an ovine model, continuous infusion of terlipressin permanently reversed endotoxin-induced systemic arterial hypotension and improved left ventricular stroke work, whereas bolus injections were associated with a decrease in cardiac index and increases in pulmonary resistance [10].

The purpose of the study by Morelli and colleagues [1] was to test this hypothesis in humans. They used a fixed low dose of continuous infusion of terlipressin (1.3 μg/kg per hour, which is approximately equal to 2 mg/day). This treatment was associated with a reduced norepinephrine infusion rate as compared with a control group. This result was not found in the vasopressin group (0.03 U/minute). However, as the fixed dosages were compared, this suggests that vasopressin at 0.03 U/minute probably reduces vasoconstriction less than terlipressin at 1.3 μg/kg per hour.

VASST = Vasopressin and Septic Shock Trial.

The use of invasive monitoring is one of the strengths of the study. As compared with norepinephrine, terlipressin did not impair systemic hemodynamics. However, the persistent low levels of mixed venous oxygen saturation (SvO_2) in all groups were quite unusual in septic shock. This would indirectly show that the management of these patients did not follow recent published guidelines [11]. The investigators should not be blamed for not following international guidelines, but a local effect may have a role in their findings. At variance, low-dose terlipressin seems to have beneficial effects on regional hemodynamics [12].

One point deserves consideration. Although vasopressin and analogs are recommended in patients with refractory septic shock, the investigators chose to introduce them as first-line treatment. This strategy may in fact be supported by several lines of evidence. In the Vasopressin and Septic Shock Trial (VASST), low-dose vasopressin plus norepinephrine was compared with norepinephrine among patients with septic shock [13]. Although low-dose vasopressin did not reduce overall mortality rates, the mortality rate in patients with less severe septic shock was lower in the vasopressin group than in the norepinephrine group. These results are consistent with findings in isolated arteries, in which the 'beneficial' synergistic effect of low-dose vasopressin (on norepinephrine responsiveness) was preserved in conditions mimicking less severe septic shock but was eliminated in a model of more severe shock [14]. Hence, one can hypothesize that a strategy using an early and multimodal approach to counteract the vascular dysfunction in septic shock may pay off.

Already, we are waiting for the results of the subsequent study, entitled Terlipressin in Septic Shock Trial (TESST-1). This randomized study, a European translation of VASST, was initiated to assess the safety and efficacy of continuous low-dose terlipressin infusion to treat patients with septic shock.

Competing interests

The author declares that they have no competing interests.

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