Commentary

Rescue therapy in septic shock – is terlipressin the last frontier?

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Published: 21 March 2006
This article is online at http://ccforum.com/content/10/2/131

Critical Care 2006, **10:**131 (doi:10.1186/cc4863)

See related research by Rodriguez-Nunez *et al.* in issue 10.1 [http://ccforum.com/content/10/1/R20]

Abstract

Use of terlipressin, an analogue of vasopressin, can be considered in septic shock patients with intractable hypotension and high cardiac output in whom fluid resuscitation and high-dose conventional catecholamines have failed. The effects of this agent on organ function are poorly evaluated in humans. The limited number of patients evaluated precludes any analysis of adverse outcomes and prognosis.

In the previous issue of *Critical Care*, Rodriguez-Nunez and coworkers [1] report their experience with terlipressin in 16 children with refractory septic shock. Over the past few years there has been much interest in the use of terlipressin in such settings, both in adults [2-6] and children [7-10].

Septic shock is a form of distributive shock characterized by arteriolar and venous vasodilatation. The objectives of treatment are twofold [11]: to maintain oxygen delivery above a critical threshold and to increase mean arterial pressure (MAP) to a level that allows distribution of cardiac index (CI) sufficient for adequate organ perfusion. Among the catecholamines, noradrenaline (norepinephrine) and dopamine are often favoured. However, vascular responsiveness to catecholamines diminishes over time, and patients may die in states of intractable shock [12]. The vascular hyporeactivity to catecholamines is caused, among other mechanisms, by excessive nitric oxide formation associated with an activation of ATP-sensitive potassium channels and reduction in calcium entry through voltage-gated calcium channels [13]. Thus, the search for alternative vasopressors is of high priority.

Vasopressin mediates vasoconstriction via V_1 receptors and increases intracellular calcium concentration. This action is not impaired during sepsis, and vasopressin has been shown to be effective in reversing catecholamine-resistant hypotension in patients with septic shock [14]. Vasopressin is not available in all countries, and some hospital pharmacies dispense lysine vasopressin, or terlipressin (Glypressine®; Ferring Company, Berlin, Germany), which is the form of vasopressin that is present in pig.

The first clinical trial evaluating the efficacy of terlipressin in septic shock was performed in a small case series of eight patients [2]. Terlipressin was administered as a single bolus of 1 mg (the dosage used in gastroenterological indications) in patients with septic shock refractory to catecholamine/hydrocortisone/methylene blue. A significant improvement in blood pressure was achieved in these patients during the first 5 hours. Cardiac output was reduced, which might have impaired oxygen delivery; no other adverse effect was observed. Partial or total weaning from catecholamines was possible.

Another study was conducted in 15 patients with catecholamine-dependant septic shock (noradrenaline ≥0.6 μg/kg per min) [5]. An intravenous bolus of 1 mg terlipressin was followed by an increase in MAP and a significant decrease in CI. Oxygen delivery and consumption were significantly decreased. Gastric mucusal perfusion was evaluated by laser Doppler flowmetry and was increased after administration of terlipressin.

In the latter study, rather low doses of noradrenaline were used (0.75 μg/kg per min at baseline) and the study patients could not really be considered 'catecholamine resistant' [5]. Such patients were evaluated by our group [4]. Terlipressin was used in patients with intractable hypotension despite use of >2.0 μg/kg per min noradrenaline and 25 μg/kg per min dopamine. In these 'catecholamine-resistant' patients, terlipressin (1 or 2 mg intravenously) was able to reverse the intractable hypotension, with a concomitant decrease in heart rate and CI. In this study oxygen delivery and consumption were significantly decreased during use of terlipressin. A similar observation was reported in sheep [15]. We cannot rule out worsened oxygen extraction and utilization in our

CI = cardiac index; MAP = mean arterial pressure.

patients. The terlipressin-induced fall in oxygen delivery and consumption emphasizes the need to monitor CI closely when this drug is used in patients with sepsis. The additional use of a potent positive inotropic drug such as dobutamine is of interest. Despite a decrease in oxygen delivery and consumption, lactate concentrations remained constant or even decreased during use of terlipressin [4,6,15]. Such a dependence on oxygen supply is usually associated with some degree of tissue ischaemia and a subsequent increase in lactate concentration. We speculated that terlipressin could have modulated the hyperdynamic metabolic response during endotoxaemia and exerted anti-inflammatory effects, thereby decreasing the oxygen needs of tissues [4].

Experience with terlipressin in children is also limited. Four studies were published prior to the start of 2006 [7-10]. Like the ones conducted in adults, these studies have serious limitations, including administration of the drug in desperate cases and evaluation of small numbers of patients. One serious concern is raised by the high incidence of ischaemia during terlipressin administration [1]. In nine patients without signs of ischaemia, five developed skin and/or limb ischaemia. Interestingly, in seven other patients with signs of ischaemia before use of terlipressin, signs of ischaemia improved in four of them. Such a heterogeneous response is intriguing and emphasizes the needed (at least in adults) for close monitoring of CI and systemic vascular resistance.

Another important consideration with use of terlipressin is its effects on regional haemodynamics and organ function. At present the evidence is limited. Renal function and gastric mucosal perfusion are improved [4-6], but no control groups were evaluated in two of these studies [4,5]. Therefore, further studies are need to determine the safety of terlipressin when used in patients with septic shock.

In conclusion, use of terlipressin may be considered in patients with (truly) refractory septic shock despite adequate fluid resuscitation and high-dose conventional vasopressors [16]. If terlipressin is a last resort therapy, then the advantages (increased MAP, and improved renal function and perfusion of gastric mucosa) should be weighed against unresolved issues, namely effects on other organs and risk for severe and irreversible ischaemia, not to mention the (unknown) effects on the microcirculation.

Competing interests

The authors declare that they have no competing interests.

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