ICU

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Treatment of Catecholamine Refractory Hypotension in Septic Shock:Beyond First-Line Vasopressor

Hypotension during septic shock is a strong indicator of patient outcome and mortality. Arginine vasopressin is a naturally produced human hormone with vasoconstriction effect via V1 receptor activation and a short 5-20 minutes half-life and is recommended by the Surviving Sepsis Campaign guidelines to be added as a second-line vasoactive agent when increasing mean arterial pressure with norepinephrine alone is not possible and/or to reduce norepinephrine dose.

Hypotension during septic shock is one of the most important indicators of 30-day outcome, including mortality (Varpula et al. 2005; Dünser et al. 2009), which is why vasoactive agent management for haemodynamic stability is an integral part of the Surviving Sepsis Campaign (SSC) guidelines (Rhodes et al. 2017).

Norepinephrine is recommended as first-line agent to increase mean arterial pressure (MAP) (Rhodes et al. 2017), but for severe septic shock patients who do not achieve target MAP despite norepinephrine (NE) infusion, arginine vasopressin is recommended as second-line vasopressor to increase MAP and reduce norepinephrine infusion (Rhodes et al. 2017). In this article, we will discuss why hypotension in certain patients become catecholamine refractory, how to identify it, and why is vasopressin recommended for such patients.

Understanding Hypotension in Septic Shock

Hypotension in septic shock can be linked to loss of vascular tone, myocardial dysfunction, or insufficient intravascular volume (Varpula et al. 2005).

Loss of vascular tone in septic shock is a major contributor of hypotension. This is linked to an increased production of nitric oxide (NO), a potent vasodilator as a result of the inflammatory response to infection (Dalimonte et al. 2020), accompanied by a drop in endogenous vasopressor production, such as vasopressin (Russell 2011) and catecholamines (Rittirsch et al. 2008).

> **impaired vascular responsiveness to catecholamines is due to downregulation or decoupling of α1 adrenergic receptors ...in such cases, vasopressors with an alternative mode of action are needed to achieve vasoconstriction and increase blood pressure**

Vasoactive agents, which can be classified into catecholamine or non-catecholamines (Dalimonte et al. 2020), activate specific receptors located on vascular myocytes, such as α_1 adrenergic and V1a receptors, which increase cytosolic calcium concentrations in vascular myocytes, leading to vasoconstriction, increasing vascular tone and consequently increasing MAP (Jentzer and Hollenberg 2020). Norepinephrine, a catecholamine, increases vascular tone by activating the α_1 adrenergic receptors and like other catecholamines (i.e. epinephrine, dopamine) also activates the ß-adrenergic receptor, such as $ß_1$ and $ß_2$.

Catecholamine Refractory Septic Shock

In certain patients, catecholamine infusion is unable to stimulate the α1 adrenergic receptors to induce vasoconstriction and increase MAP. This impaired vascular responsiveness to catecholamines is due to downregulation or decoupling of α1 adrenergic receptors (Jentzer and Hollenberg 2020), primarily caused by lactic acidosis (Rittirsch et al. 2008). This could be identified by persistent hypotension despite norepinephrine infusion of >0.2-0.3µg/kg/min combined with infusion of fluids and adequate or high cardiac output (Jentzer and Hollenberg 2020) indicative of catecholamine refractory septic shock.

In such cases, non-catecholamine vasopressors with an alternative mode of action are needed to achieve vasoconstriction and increase blood pressure.

Arginine Vasopressin as Second-line Vasopressor

Arginine vasopressin, also known as vasopressin, argipressin, and anti-diuretic

hormone, is a naturally produced human hormone and a non-catecholamine vasopressor. It achieves vasoconstriction by activating the V1a receptors and as a result can increases blood pressure and MAP (Dünser 2013). Based on that, arginine vasopressin is recommended by the SSC guidelines to be added as a second-line vasoactive agent (0.01-0.03IU/min) when increasing mean arterial pressure with norepinephrine alone is not possible, and/or to reduce catecholamine infusion (Rhodes et al. 2017). Unlike synthetic vasopressin analogs, which have an 8-hour half-life, arginine vasopressin has a half-life of 5-20 minutes only. This short effective half-life provides a high degree of control, as the vasopressor effect could be quickly halted once infusion is discontinued in case of unwanted side-effects (Tanja et al. 2006).

The early combination of arginine vasopressin has also shown to decrease the need for Renal Replacement Therapy (RRT) by 55% for septic shock patients at risk of renal failure (1.5x serum creatine based on the RIFLE criteria) and reduce the progression to renal failure (Gordon et al. 2010).

In a systematic review of 23 randomised controlled trials (3088 patients), the addition of arginine vasopressin to catecholamine vasopressors compared with catecholamines alone was associated with a lower risk of atrial fibrillation (RR, 0.77) (McIntyre et al. 2018). This can be related to a reduction in adrenergic stimulation provided by the catecholamine sparing effect of arginine vasopressin.

Additionally, arginine vasopressin does not seem to constrict pulmonary arteries, as at low doses (0.01-0.03 IU/min) arginine vasopressin causes endothelial nitric oxide release in pulmonary arteries, when V1a receptors are activated (Currigan et al. 2014; Chan et al. 2015; Holmes et al. 2004).

Arginine vasopressin is marketed by AMOMED under the following brand names: Empressin®, Embesin®, Embesyn®, Empesin®, Empressine® and ReverPleg®. For more information regarding the product, please visit amomed.com. ■

Key Points

- Septic shock patients suffering from hypotension despite >0.2-0.3µg/kg/min of norepinephrine infusion combined with fluid administration and high adequate cardiac function is indicative catecholamine refractory septic shock.
- Arginine vasopressin is a naturally produced human hormone with vasoconstriction effect via V1 receptor activation and a short 5-20 minutes half-life.
- Arginine vasopressin is recommended by the SSC Gudielines as a second-line vasopressor to increasing mean arterial pressure and reduce norepinephrine dose.
- The early combination of arginine vasopressin has shown to decrease the need for Renal Replacement Therapy.
- The addition of arginine vasopressin to catecholamine vasopressors compared with catecholamines alone was associated with a lower risk of atrial fibrillation.

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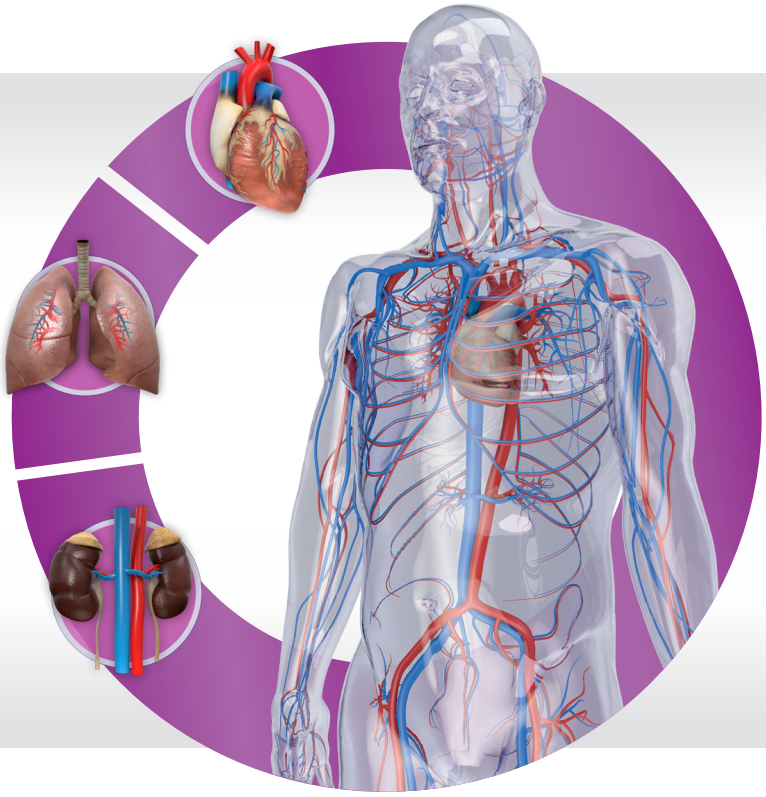
Treating Catecholamine Refractory Hypotension in Septic Shock



Increase mean arterial pressure
in catecholamine refractory septic shock[1,3]

Reduce Norepinephrine Infusion
while maintaining mean arterial pressure[1,2]

Increase Chances of Survival
for patients with less severe septic shock (<15µm/min NE)[5] and patients at risk of AKI (increased serum creatinine x1.5)[4]

NAME OF THE MEDICINAL PRODUCT: Empressin 40 I.U./2 ml concentrate for solution for infusion. **QUALITATIVE AND QUANTITATIVE COMPOSITION**: One ampoule with 2 ml concentrate for solution for infusion contains argipressin acetate corresponding to 40 I.U. argipressin (equating 133 microgram). 1 ml concentrate for solution for infusion contains argipressin acetate corresponding to 20 I.U. argipressin (equating 66.5 microgram). Excipients with known effect: Each ml contains less than 23 mg of sodium. **List of excipients:** Sodium chloride, glacial acetic acid for pH adjustment, water for injections. **Therapeutic indications**: Empressin is indicated for the treatment of catecholamine refractory hypotension following septic shock in patients older than 18 years. A catecholamine refractory hypotension is present if the mean arterial blood pressure cannot be stabilised to target despite adequate volume substitution and application of catecholamines (see section 5.1 of the published SmPC). **Pharmacotherapeutic group:** Vasopressin and analogues, ATC code: H01BA01. **Contraindications**: Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the published SmPC. **Nature and contents of container.** Clear glass ampoules (Type I, with a broken ring on the narrow part of the ampoule) with 2 ml concentrate for solution for infusion. Pack sizes: 5 and 10 ampoules. Not all pack-sizes may be marketed. **MARKETING AUTHORISATION HOLDER:** Orpha-Devel Handels und Vertriebs GmbH, Wintergasse 85/1B, 3002 Purkersdorf, Austria **DATE OF REVISION OF THE TEXT:** 02/2018. **Prescription status/ Delivery by pharmacies:** Prescription only medicine/ Pharmacy-only. For information on undesirable effects, special warnings and precautions for use, interaction with other medicinal products and other forms of interaction, use in pregnancy and lactation and impact on fertility please refer to the published SmPC.

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