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A Review on Pharmacology of Septic Shock

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ABSTRACT

Shock is an acute, generalized state of inadequate perfusion of critical organs that can produce serious pathophysiologic consequences, including death, when therapy is not optimal. Shock is defined as systolic blood pressure <90 mm Hg or reduction of at least 40 mm Hg from baseline with perfusion abnormalities despite adequate fluid resuscitation. Continuous hemodynamic monitoring with an arterial catheter or a central venous catheter capable of measuring mixed venous oxygen saturation (SVO2) or central venous oxygen saturation (S CVO2) should be used early and throughout the course of septic shock to assess intravascular fluid status and ventricular filling pressures, determine cardiac output (CO), and monitor arterial and venous oxygenation. They can be used for monitor the response to drug therapy and guiding dosage titration.

Keywords: septic shock, Dopamine, Vassopressins, perfusion, systolic blood pressure

INTRODUCTION

Shock is an acute, generalized state of inadequate perfusion of critical organs that can produce serious pathophysiologic consequences, including death, when therapy is not optimal. Shock is defined as systolic blood pressure <90 mm Hg or reduction of at least 40 mm Hg from baseline with perfusion abnormalities despite adequate fluid resuscitation. 1 Previously, mortality from septic or cardiogenic shock exceeded 70% but now ranges between 30% to 50% , the theory and current status of hemodynamic monitoring and presents an update on the optimal use of inotropes and vasopressor drugs in shock states, specifically septic shock.

Hemodynamic and perfusion monitoring can be categorized into two broad areas: global and regional monitoring. Global parameters, such as systemic blood pressure and pulse oximetry, assess perfusion and oxygen utilization of the entire body. Regional monitoring techniques, such as tonometry, focus on oxygen delivery and subsequent changes in metabolism of individual organs and tissues

USE OF VASSOPRESSORS AND INOTROPED IN THE PHARMACOLOGY OF SHOCK

Vasopressors and inotropes in patients with septic shock are required when volume resuscitation fails to maintain adequate blood pressure (MAP ≥65 mm Hg) and organs and tissues remain

hypoperfused despite optimizing CVP to 8 to 12 mm Hg or PAOP to 12 to 15 mm Hg. 7 However, vasopressors may be needed temporarily to treat life-threatening hypotension when filling pressures are inadequate despite aggressive fluid resuscitation. Inotropes are frequently used to optimize cardiac function in cases of cardiogenic shock. The clinician must decide on the choice of agent, therapeutic end points, and safe and effective doses of vasopressors and inotropes to be used. This section reviews adrenergic receptor pharmacology, exogenous

catecholamine use, and alterations in receptor function in critically ill patients. It also provides guidelines for the clinical use of adrenergic agents, optimization of pharmacotherapeutic

outcomes, and minimization of adverse effects in critically ill patients with septic shock. Therapies of hypovolemic shock and cardiogenic shock are discussed in other chapters.

Of note, agents other than catecholamines have been used as inotropes and vasopressors in shock states. They include phosphodiesterase III inhibitors, naloxone, nitric oxide (NO) synthase

(NOS) inhibitors and calcium sensitizers. This chapter focuses on catecholamines. Vasopressin and corticosteroids, as they relate to septic shock, also are emphasized because they have pharmacologic interactions with catecholamines, possess hemodynamic effects, and are frequently used.

Dopamine frequently is the initial vasopressor used for patients with septic shock. 6 – 19 , 67 Dosages of 5 to 10 mcg/kg/min are initiated to improve MAP. Most studies of patients with septic shock have shown that dopamine at these doses increases the cardiac index by improving contractility and heart rate, primarily from its β 1 effects. It increases MAP and SVR as a result of both increased CO and, at higher doses (>10 mcg/kg/min), its α 1 effects.

The clinical utility of dopamine as a vasopressor in the setting of septic shock is limited because large dosage rates frequently are necessary to maintain CO and MAP. At dosages exceeding 20 mcg/ kg/min, further improvement in cardiac performance and regional hemodynamics is limited. Its clinical use frequently is hampered by tachycardia and tachydy arhythmias, which may lead to myocardial ischemia. Although tachydy ahythmias theoretically should not be expected to occur until administration of dopamine 5 to 10 mcg/ kg/min, these β 1 effects are observed with dosages as low as 3 mcg/ kg/min. They seem to be more prevalent in patients who are inadequately resuscitated (hypovolemic), in the elderly, in those with preexisting or concurrent cardiac ischemia or dysrhythmias, and in patients currently receiving other dysrhythmogenic agents, including vasopressors and inotropes.

EFFECT OF DOPAMAINE IN SHOCK

Dopamine increases PAOP and pulmonary shunting to decrease Pao2 . The increase in PAOP may be due to changes in diastolic volumes from decreased cardiac compliance or increased venous return to the heart by α -adrenergic receptor–mediated venoconstriction. This may affect gas exchange and decrease Pa o 2 . The increase in pulmonary shunting also may result from acute enhancement of pulmonary blood flow to nonhomogeneous lung regions. Thus, dopamine should be used with caution in patients with elevated preload because the drug may worsen pulmonary edema. In the instance of high filling pressures, tachycardia, or tachydysrhythmias, dopamine should be replaced by another vasopressor and/or inotrope such as norepinephrine, dobutamine, phenylephrine, or epinephrine, depending on the desired effect. The effect of dopamine on global oxygen-transport variables parallels the hemodynamic effects. Although dopamine improves global D o 2 in septic patients, it may compromise O 2 ER in the splanchnic and mesenteric circulations by α 1 - mediated vasoconstriction. Splanchnic blood flow and D o 2 increase with dopamine, but with no preferential increase in splanchnic perfusion as a fraction of CO and systemic increases in D o 2 . Large doses of dopamine worsen pHi and the P co 2 gap. This is reflected by a decrease or lack of change in regional V o 2 and a decrease in tissue O 2 ER. Dopamine at low or vasopressor dosages directly impedes gastric motility in critical illness and may aggravate gut ischemia in septic shock. Similar to high-dose administration, low-dose dopamine increases splanchnic blood flow but lowers splanchnic V o 2 in sepsis. Therefore, dopamine at all dosages impairs hepatosplanchnic metabolism despite an increase in regional perfusion.The use of dopamine as a first-line agent for septic shock maybe questionable because regional hemodynamics, oxygen- variables, and functional parameters of improved organ perfusion are not consistently enhanced in a sustained manner and may be negatively impaired. 7 , 63 The negative findings of low-dose dopamine use (see Low (“Renal”) Dose Dopamine above) and the deleterious effects of inotropic and vasopressor dosages of dopamine on regional hemodynamics and oxygen transport raise concern over whether dopamine should be considered the first-line vasopressor agent in patients with severe

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sepsis or septic shock. 7 , 7 , 79 Until dopamine is found to have definitive deleterious clinical outcomes compared to other vasopressors, empirical use of dopamine in a hypotensive patient in whom a pulmonary arterial catheter has not been inserted and in whom the cause of hypotension—low CO or vasodilation—is yet undetermined still may be reasonable. In addition, unlike other vasopressor agents, dopamine is available as premixed ready-to-use solutions of various concentrations that can be stored in automated dispensing systems for rapid initiation.

OTHER THERAPIES

As with vasopressin and cortisol, critical illness impairs hypothalamic– pituitary function, producing relative deficiencies of triiodothyronine (T 3) and thyroxine (T 4). This condition, referred to as *euthyroid sick syndrome* , may contribute to hypotension. 89 Concentrations of thyrotropin-releasing hormone and thyroidstimulating hormone are inappropriately low. Measured concentrations of free T 3 and T 4 may be low or normal, but synthesis is consistently impaired. Only scant data regarding the replacement of these hormones in critically ill patients are available, and the results are variable, depending on the extent of additional hormone replacement (growth hormone, gonadotropin-releasing hormone, leptin, insulin, thyrotropin-releasing hormone, and thyroid-stimulating hormone). Given the data for replacing vasopressin and cortisol in septic shock, it is reasonable to assume that one day a "thyroid replacement" regimen will be offered as an adjunctive treatment to vasopressors.

Drotrecogin alfa (activated) or recombinant activated protein C has been established as a treatment of severe sepsis because it reduces mortality when used early in patients with at least two organ dysfunctions or an Acute Physiology and Chronic Health Evaluation (APACHE) II score of 25. 90 Drotrecogin alfa (activated) promotes fibrinolysis, inhibits coagulation, and modulates inflammation. It inhibits inflammation, possibly preventing endotoxin-induced hypotension. A study of 22 septic shock patients treated with drotrecogin alfa (activated) showed that the norepinephrine dosage rate decreased 33% over 24 hours. 91 In contrast, the norepinephrine dosage increased 38% in the matched control group despite MAP values similar to the drotrecogin alfa (activated)group. Although these results deserve further investigation, drotrecogin alfa (activated) likely will never be administered solely for hemodynamic support of septic shock patients because it is an expensive agent with concerns of hemorrhage as a side effect. Ultimately, patients who "qualify" for drotrecogin alfa (activated) will receive it irrespective of hemodynamic effect.

RESUSCITATION OF SEPTIC SHOCK

Initial hemodynamic therapy for septic shock is the administration of intravenous fluid (20–40 mL/kg of crystalloid fluid), with the goal of attaining CVP of 8 to 12 mm Hg or 15 mm Hg in mechanically ventilated patients or patients with abdominal distension or preexisting ventricular dysfunction. 6 – 19 , 30 Crystalloid fluids (e.g., normal saline, Ringer lactate) and colloid fluids (e.g., albumin, hydroxyethyl starch, blood products) are considered equivalent for shock resuscitation. 65 Crystalloid fluids are generally preferred unless patients are at risk for adverse events from redistribution of intravenous fluids to extravascular tissues and/or are fluid restricted (e.g., patients with renal dysfunction, decompensated heart failure, ascites compromising diaphragmatic function). 7 Recent data suggest hydroxyethyl starch may increase the risk of acute renal dysfunction in a dose-dependent manner and possibly enhance mortality. 66 Its use warrants caution.

ADVERSE EFFECTS:

Catecholamine vasopressors may result in adverse peripheral vasoconstrictive, metabolic and dysrhythmogenic effectsthat limit or outweigh their positive effects on the central circulation. Norepinephrine, phenylephrine, and epinephrine can produce lactic acidosis secondary to excessive constriction in peripheral arterioles or enhanced glycogenolysis, or as a result of mobilization of lactate from peripheral tissues as a result of improved oxygenation.

Additionally, excessive peripheral vasoconstriction may cause ischemia or necrosis of already poorly perfused tissues such as the skin and the mesenteric and splanchnic circulations. Some of these profound vasoconstrictive effects have been compounded by the concurrent use of other vasopressor agents in

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patients with septic shock who are significantly hypovolemic. These agents may be used in the context of late septic shock, where hypotension is refractory to less selective vasoconstrictors (e.g., dopamine) such that very large doses of norepinephrine or epinephrine or phenylephrine are required but provide little or no benefit. Myocardial ischemia and dysrhythmias may occur in patients with coronary artery disease, atherosclerosis, cardiomyopathies, left ventricular hypertrophy, congestive heart failure, or underlying dysrhythmias because of their inability to tolerate β 1 cardiac stimulation that mediates increases in CO. However, the effect usually is opposite in healthy myocardium and in young patients. β 1 Cardiac stimulation is well tolerated, ventricular filling pressures decrease, and CO and Do2 increase, with a resulting increase in peripheral perfusion.

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