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ICU Director 2013 4: 88 originally published online 25 February 2013

DOI: 10.1177/1944451613477659

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CLINICAL CASE REPORT

Cardiovascular Collapse in Anaphylaxis Successfully Treated With Vasopressin

Case Report and Review of Mechanism

Patricia Weott CRNA, MSN¹

Abstract: In this report, we describe the case of a 52-year-old man who suffered a severe anaphylactic reaction in the operating room that was unresponsive to epinephrine. After an uneventful induction and intubation, he received antibiotics and was placed in the prone position. His blood pressure began to decline and despite escalating doses of phenylephrine, ephedrine, and then epinephrine, his pressure continued to deteriorate and became unobtainable. When all other resuscitative measures failed, a single dose of vasopressin 20 units was given intravenously; the patient had an immediate response with dramatic reversal of the cardiovascular collapse. He was then stabilized, transferred to the ICU, and subsequently discharged home without neurologic sequelae. In this article, we review the signs and symptoms of anaphylaxis seen in patients under anesthesia and consider the pathophysiologic mechanisms of the reaction that support the use of vasopressin.

Keywords: anaphylaxis, vasopressin, shock, allergy, nitric oxide, K_{ATP} channels

Introduction

Control of the airway and administration of oxygen, catecholamines, fluids, antihistamines, and corticosteroids have long been the standard treatments of anaphylaxis. These basic supportive measures do not address all the pathophysiologic pathways that can be activated in an anaphylactic reaction. What may be left unaddressed by these approaches are other root causes of cardiovascular collapse such as hyperstimulation of nitric oxide-generating pathways, activation of adenosine-5'-triphosphate (ATP)-sensitive potassium (K^+) channels (K_{ATP} channels), and low circulating levels of vasopressin. Epinephrine is the drug of choice in anaphylaxis but it

may fail to affect these pathways. Vasopressin, whose mechanisms of action precisely match these additional causative factors associated with the profound hypotension of anaphylaxis, may have a unique role in its treatment. This case study will describe the efficacy of vasopressin in severe anaphylactic shock with cardiovascular collapse that was unresponsive to epinephrine.

Case Report

History

A 50-year-old American Society of Anesthesiology (ASA) class II male weighing 104 kg was scheduled for a wide excision of upper back melanoma and sentinel lymph node dissection in the prone position. Past surgical history included general anesthesia in 1999

for arthroscopic knee surgery without complication and a biopsy with local resection of a melanoma of the back. His past medical history and review of systems were noncontributory.

The patient was not on any medication and he denied any known drug allergies but he did have a sensitivity to poison oak. He had received antibiotics in the past without problems, including a course in the past 6 months for a dental procedure. His family history was

“VASOPRESSIN, WHOSE MECHANISMS OF ACTION PRECISELY MATCH THESE ADDITIONAL CAUSATIVE FACTORS ASSOCIATED WITH THE PROFOUND HYPOTENSION OF ANAPHYLAXIS, MAY HAVE A UNIQUE ROLE IN ITS TREATMENT.”

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noncontributory except for his father who had an anaphylactic reaction to red meat. It was suggested, but never proven, that this was related to an antibiotic allergy.

Anesthetic Management

The patient was seen in the preoperative holding area and received versed 2 mg intravenous (IV). He was brought into the operating room and baseline vital signs were blood pressure (BP) of 120/73 mm Hg, heart rate (HR) 64, and oxygen saturation (Spo₂) of 99%. The patient was preoxygenated and anesthesia induced with IV fentanyl 200 µg and propofol 200 mg. Muscle relaxation was obtained with rocuronium 50 mg and the trachea was intubated without difficulty. Desflurane 4.5% to 6.0% was administered for anesthetic maintenance. His postinduction vital signs were stable with a BP 118/64 mm Hg, HR 64, and Spo₂ 100%. The patient was then placed in the prone position and given cefazolin 2 g IV per perioperative prophylactic antibiotic protocol. As the surgical team was preparing for incision, the blood pressure began to drop and despite administration of multiple doses of phenylephrine (500 µg total) and ephedrine (20 mg total) IV the patient's vital signs did not improve. The blood pressure continued to decrease and epinephrine was given as an initial bolus dose of 300 µg. After the epinephrine was given, HR increased from 80 to 120 but his blood pressure showed no improvement. Despite additional epinephrine boluses, BP continued to fall rapidly and ultimately became unobtainable. Despite the absence of noninvasive blood pressure reading, weak carotid and femoral pulses were palpable. In addition, there was neither digital reading nor waveform present on the pulse oximeter monitor after the blood pressure became unobtainable. When it became evident that his blood pressure would not respond to catecholamines, the surgical procedure was aborted, the patient was turned back to the supine position. Once turned, a survey of his physical appearance revealed severe angioedema of the face and widespread erythema and swelling over the body. A tentative diagnosis of anaphylactic shock was made and an anaphylaxis protocol was initiated. The epinephrine dose was increased to 1 mg boluses (3.5 mg total), and hydrocortisone 300 mg, diphenhydramine 50 mg, and famotidine 20 mg were given IV. An external jugular intravenous line was started and fluids were given as rapidly as possible. The end tidal CO₂ reading was 12 mm Hg. Several attempts at inserting an arterial line at this time were unsuccessful.

After approximately 10 minutes without response to any medication, vasopressin 20 units IV was given. The BP immediately improved and rose to 90 mm Hg systolic followed by a reading of 120 mm Hg. The electrocardiogram from the monitor showed sinus tachycardia converting to a junctional rhythm with aberrances and then stabilizing in a normal sinus rhythm. An arterial line and a femoral line were inserted. The patient had received approximately 6 L of resuscitative fluids and the initial central venous pressure reading was 13 mm Hg. Blood samples sent for analysis at this point showed elevated tryptase levels greater than ten times normal. An arterial blood gases (ABG) returned with pH 7.22, pCO₂ 58 mm Hg, po₂ 141 mm Hg,

and a base excess of -5 on 100% Fio₂. On restoration of blood pressure and initial stabilization, the patient was transferred to the ICU and remained intubated on epinephrine and propofol infusion.

In the ICU, vital signs were stable and the epinephrine was quickly weaned off. At 11:00 PM that evening, an ABG showed a pH of 7.18. A repeat ABG showed worsening metabolic acidosis with a pH of 7.14. The combination of the high-dose catecholamines, propofol infusion, and the progressive acidosis strongly suggested likelihood of propofol infusion syndrome. The propofol drip was immediately discontinued and the acidosis improved without further problems. The patient remained intubated in the ICU for 2 days because of fluid shifts and was extubated on the third hospital day. He was subsequently discharged home in stable condition on postanesthesia day 7.

The patient was seen for follow-up care in the allergy/immunology clinic. The exact culprit of his anaphylaxis could not be positively identified, but rocuronium and cefazolin were suggested as the probable causes. He was counseled to list these drugs as anaphylactic allergies. He subsequently returned for surgical excision of his melanoma without problem.

Discussion

The earliest known reported fatality from allergy was that of King Menses of Egypt who died from the sting of a wasp sometime between 3640 and 3300 BC. Portier and Riche first coined the term anaphylaxis in 1902 to describe the syndrome of shock and subsequent death that occurred in dogs following reinjection of the poison of the sea anemone.¹ Today, the occurrence of anaphylaxis during anesthesia is estimated to be between 1:3500 and 1:20 000 with a reported mortality of 4% and an additional 2% surviving with brain injury.² In the United States, there are approximately 84 000 cases of anaphylaxis each year with 840 deaths.³

Anaphylaxis can be defined as an acute multi-organ system reaction, potentially fatal, caused by the release of chemical mediators from mast cells and basophils. Various adjectives such as unanticipated, unpredictable, explosive, lethal, and morbid have been used to characterize the anaphylactic reaction. In the operating room, the most frequently implicated causes of anaphylaxis are muscle relaxants (69%), natural rubber latex (12%), antibiotics (8%), and induction agents (4%).⁴ Since prompt recognition and treatment of anaphylaxis is imperative, conditions that mimic allergic reactions need to be excluded. Septic shock, hypovolemic shock, foreign body in the airway, cardiogenic shock, and vasovagal reaction are a few of these conditions (Table 1).⁵

The manifestations of anaphylaxis result from the immune-stimulated release of mediators, including histamine, prostanooids, leukotrienes, kinins, and platelet-activating factor. Table 2 provides an overview of these mediators and the kinds of effects they can produce.⁵

Anaphylaxis may strike so quickly that early signs of the reaction are often unrecognized; cardiovascular collapse is often the sole presentation, occurring in 50% of cases.⁶ Leakage

Table 1. Differential Diagnosis for Symptoms Seen in Anaphylaxis

Presentation	Differential Diagnosis
Hypotension	Septic shock
	Vasovagal reaction
	Cardiogenic shock
	Hypovolemic shock
Respiratory distress with wheezing or stridor	Airway foreign body
	Asthma/chronic obstructive pulmonary disease
	Vocal chord dysfunction syndrome
Postprandial collapse	Airway foreign body
	Monosodium glutamate ingestion
	Sulfite ingestion
	Scombroid fish poisoning
Flush syndrome	Carcinoid
	Postmenopausal hot flashes
	Red man syndrome (vancomycin)
Miscellaneous	Panic attacks
	Systemic mastocytosis
	Hereditary angioedema
	Leukemia with excess histamine production

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of plasma from capillaries due to increased permeability is one of the predominate factors of circulatory collapse. As a result, the circulating blood volume may decrease by as much as 35% within minutes, causing decreased preload, hypotension, tissue hypoperfusion, and cellular anoxia.⁷

Besides increased vascular permeability, additional cellular and molecular mechanisms have been identified in anaphylactic cardiovascular collapse:

- *Activation of the inducible form of nitric oxide (NO).* In anaphylaxis overstimulation of nitric oxide synthase expressed in the endothelium (eNOS) can generate copious amounts of NO. This overproduction causes profound relaxation of smooth muscle resulting in resistant hypotension and death.³
- *Activation of the ATP-sensitive potassium (K_{ATP}) channels.* In their inactive state, K_{ATP} channels are physiologically closed, that is, nonconductive. In anaphylaxis, physical factors generated by the reaction, such as increased lactate and decreased intracellular and extracellular pH stimulate opening of K_{ATP} channels resulting in K^+ efflux from cells. The ensuing cell membrane hyperpolarization inactivates voltage-gated calcium channels leading to a fall in cytosolic calcium levels. Vascular smooth muscle cell relaxation contributes to the profound vasodilatory effect that ensues.⁸
- *Deficiency of the vasopressin hormone.* Hypotension directly stimulates vasopressin release through activation of aortic and carotid baroreceptors. In the initial shock state, high circulating levels of vasopressin can be measured but as hypotension persists, vasopressin levels may become inappropriately low.^{8,9} The reasons behind this deficiency may be exhaustion of secretory stores in the posterior pituitary and hypothalamus or impaired autonomic function.¹⁰

Epinephrine Versus Vasopressin in the Treatment of Anaphylaxis

Since the 1920s, epinephrine has been the treatment of choice for anaphylaxis and its associated hypotension.⁷ Its usefulness is first because of its powerful vasopressor actions and second, because of its ability to inhibit the release of chemical mediators, suspending the allergic reaction and reversing vasodilation.¹¹ Epinephrine is a potent stimulant of both alpha- and beta-adrenergic receptors. Alpha-adrenergic stimulation by epinephrine counteracts vasodilation and increased vascular permeability, whereas the beta-adrenergic effect relaxes bronchial smooth muscle and helps alleviate bronchospasm. These receptors also work on the heart to enhance coronary blood flow and increases cardiac output to increase blood pressure.

Although there are no contraindications to the use of epinephrine in the treatment of anaphylaxis, possible detrimental effects include increased myocardial workload and oxygen demand, myocardial infarction and ventricular arrhythmias. Most important, epinephrine alone may fail to reverse anaphylactic cardiovascular collapse, as we observed in this case. Several papers have reported positive outcomes by using vasopressin in epinephrine-resistant anaphylactic shock. Hussain et al,⁴ in 2008, described a 24-year-old woman with cardiovascular collapse in anaphylaxis that responded to 2 units of vasopressin. Williams et al,¹² in 2003, described successful resuscitation with 5 units vasopressin for a 57-year-old woman in aprotinin-induced anaphylaxis unresponsive to epi-

Table 2. Mast Cell and Basophil Major Mediator Actions

Mediators and Pathophysiologic Effects
<i>Histamine:</i> H1—Mucus secretion, edema, cardiac depression, coronary vasoconstriction, renin release; H2—gastric acid secretion, nitric oxide induction, vasodilatation, tachycardia; H3—decreased norepinephrine level; H4—chemotaxis, inflammation
<i>Heparin:</i> Anticoagulation, activates prekallikrein and contact systems, bradykinin
<i>Tryptase:</i> Activates prekallikrein and complement, bradykinin, anaphylatoxins
<i>Chymase:</i> Renin production, compensatory norepinephrine secretion, dysrhythmias
<i>Carboxypeptidase A:</i> Prostaglandin and leukotriene synthesis, inflammation
<i>Platelet-activating factor:</i> Bronchoconstriction, decreased coronary blood flow and contractility, nitric oxide induction, vasodilatation, hypotension, platelet aggregation, recruitment of neutrophils and eosinophils, biphasic late response, anticoagulation
<i>Prostaglandin D₂:</i> Bronchoconstriction, pulmonary and coronary vasoconstriction, peripheral vasodilatation, vascular permeability, hypotension, flushing, urticaria
<i>Leukotriene:</i> LTC ₄ —Bronchoconstriction, airway remodeling, angioedema, nitric oxide induction, increased vascular permeability, hypotension
<i>Kallikrein:</i> Renin production, complement activation, fibrinolysis, clotting
<i>Tumor necrosis factor:</i> Neutrophil activation, chemokines, cytokines, effector cell recruitment

Source. Reprinted with permission from AANA(2012; 80[2]:132 from Table 1 Major Mediator Actions of Mast Cells and Basophils Implicated in Anaphylaxis by C. Norred CRNA PhD. Copyright 2012 AANA Journal Course Update for Nurse Anesthetist.¹¹

nephrine. In 2008, Di Chiara et al⁹ published a case study of a 6 year-old pediatric patient with suspected heparin anaphylaxis that responded to a vasopressin infusion of 0.0003 units/kg/min after epinephrine proved futile. Finally, in 2008, Schummer et al⁷ briefly described 6 separate cases of catecholamine-resistant anaphylaxis successfully treated with vasopressin.

Vasopressin is a hormone secreted from the posterior pituitary. Under normal conditions, the major physiological role of vasopressin is the regulation of water balance.^{13(pp431-432)} In shock states, however, hypotension stimulates additional release of vasopressin to act on 3 different vasopressin subtypes, V1 (vascular), V2 (renal), and V3 (pituitary/oxytocin).¹⁴

The most widely expressed subtype is the V1 receptor, found in vascular smooth muscle, myometrium, bladder, platelets, renal medullary interstitial cells, and in many central nervous system structures. V1 receptors are responsible for vasoconstriction; their activation leads to increased levels of the second messengers inositol trisphosphate and diacylglycerol, which in turn activate voltage-gated calcium channels. The result is increased intracellular calcium levels and vasoconstriction.¹⁰ V2 receptors are predominately located in principle cells of the renal collecting duct system where

they regulate water channels and V3 receptors help mediate uterine contractions during labor.¹⁴

It is theorized that vasopressin works in profound shock to restore blood pressure by extinguishing the activation of the pathways described above. These actions include decreased synthesis of inducible NO via direct inactivation of K_{ATP} channels in vascular smooth muscle, blocking the target enzyme of the NO pathway and blunting the increase in cyclic guanosine monophosphate-induced NO. Vasopressin also potentiates the effects of other adrenergic and vasoconstrictor agents and inhibits the inflammatory cytokine interleukins.¹⁵

The same pathways implicated in the profound hypotension in anaphylaxis have also been implicated in the pathophysiology of septic shock: NO pathways, excessive activation of potassium channels, and low vasopressin levels. Buckley et al,¹⁶ in 2006, reported that the vascular hyporeactivity in septic shock will respond to vasopressin or a NOS synthase inhibitor. They stated, "Their actions are likely, at least in part, to result from closure of the vascular smooth muscle (K_{ATP}) channel."

A vasopressin dose of 0.08 U/kg has been demonstrated to be effective in restoring hemodynamic stability and improving survival in an animal model of anaphylactic shock.⁸ The dose of vasopressin cited in published articles to treat severe hypotension range from as low as 2 units⁴ to 20 units as was used in the case described here. Advanced cardiac life support guidelines do not contain an algorithm specifically for anaphylaxis but in pulseless ventricular tachycardia/fibrillation guideline, a vasopressin dose of 40 units is suggested.¹⁷

Vasopressin can affect all major systems adversely. The adverse cardiovascular side effects include cardiac arrest, decreased cardiac output, increased venous thrombosis, and myocardial ischemia. Adverse respiratory effects include bronchoconstriction and pulmonary edema. The renal side effects include myoglobinuria with acute renal failure. Adverse gastrointestinal effects include small bowel necrosis due to the thrombosis of the superior mesenteric artery. Portal vein thrombosis has been associated with arterial drug infusions for gastrointestinal hemorrhage.¹⁸

Conclusion

Profound hypotension leading to cardiovascular collapse in anaphylaxis is due to complex pathophysiologic interactions involving increased vascular permeability, escalation of the NO pathways, activation of K_{ATP} channels, and deficiency of circulating vasopressin. If this downward spiral is not stopped and reversed, death or significant morbidity such as brain damage can occur. Although not a causative factor, prone-position pressure dysregulation may have contributed to the initial hypotension. Impediment of arterial filling due to mechanical compression of the thorax and abdomen and reduction of stroke volume associated with reflex activation of the sympathetic nervous system are 2 theories of this phenomenon.¹⁹ This case demonstrated the successful use of vasopressin to reverse cardiovascular collapse in catecholamine-resistant anaphylaxis, possibly saving the patient from dire consequences. In the case of an anaphylactic reaction in the operating room, it is vital to immediately recognize it and begin treatment and also to have a thorough understanding of vasopressin and its role in the treatment of anaphylaxis.

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