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Case report on intravenous octreotide for the treatment of intraoperative vasoplegia following thymoma resection

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Abstract

Octreotide is a somatostatin analog known for its role in the treatment of acute variceal bleeding, enterocutaneous fistula and carcinoid syndrome. The reduction of portal pressure from splanchnic vasoconstriction has been attributed to the inhibition of nitric oxide synthesis, guanylate cyclase and release of glucagon. Octreotide has many therapeutic applications as a result of the ubiquitous nature of somatostatin receptors throughout the body. The effects of octreotide on vascular tone make it potentially useful in the treatment of intraoperative vasoplegia, hypotension with low systemic vascular resistance with preserved cardiac output that is refractory to adrenergic agonists. We present a case in which a patient undergoing thymoma resection developed vasoplegia that was effectively treated with octreotide. We believe that this case illustrates the need for further investigation on the potential efficacy of octreotide as an adjunct for the treatment of vasoplegia and other forms of shock.

Keywords

Octreotide, non-adrenergic vasopressors, thymoma, vasoplegia, refractory hypotension, shock

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Introduction

In contrast to routine perioperative hypotension, vasoplegia is a state of low systemic vascular resistance (SVR) accompanied by preserved cardiac output that is refractory to adrenergic agonists.[1] Endothelial dysfunction from acidemia, adrenal insufficiency, vasoactive amines or other physiologic derangements can result in decreased effectiveness of adrenergic vasopressors. Vasopressin, methylene blue and octreotide operate outside of typical adrenergic pathways and are potential treatment options when vasoplegia is present. In the appropriate setting, octreotide can simultaneously increase cardiac output, vascular resistance and the effectiveness of exogenous catecholamines. Similar to methylene blue, this combination of effects makes octreotide uniquely useful in the treatment of vasoplegia and other forms of shock. We present a case in which a patient undergoing thymoma resection developed sudden and severe vasoplegia that was effectively treated with octreotide. Per institutional policy, the approval of the Institutional Review Board was not required for this case report. Written consent was obtained from the patient and documented in the medical record.

Case description

A 68-year-old woman with stage 3a thymoma of the anterior mediastinum was admitted for complete thymectomy by sternotomy and mediastinal lymphadenectomy. She had completed three cycles of cisplatin, doxorubicin, cyclophosphamide and prednisone 2.5 months prior to surgery. Her past medical history was significant for asthma, hypothyroidism and asymptomatic pulmonary embolism being treated with enoxaparin. The patient had good functional capacity without overt cardiac disease. Significant home medications included enoxaparin, salmeterol and fluticasone. Preoperative vital signs were within normal limits.

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Induction of general anesthesia was uneventful and a double-lumen endobronchial tube was placed for lung isolation. General anesthesia was maintained with inhaled desflurane and intravenous ketamine. The patient was given intravenous dexamethasone 10 mg and ampicillin–sulbactam per routine institutional practice. The patient's vital signs throughout surgical dissection and tumor mobilization were stable, with mean arterial pressure (MAP) ranging from 60 to 110 mmHg with a heart rate (HR) 60–80 beats per minute (bpm). The thymoma was excised without vascular or cardiac injury. Over the 10-min period following tumor resection, the patient's MAP decreased from 80 to 35 mmHg, confirmed by both arterial line and noninvasive blood pressure (NIBP) cuff with a slight decrease in capnography. There was no evidence of significant surgical bleeding or pneumothorax but the heart appeared underfilled by visual inspection despite seemingly adequate volume resuscitation. Over a 20-min period, the patient remained hypotensive with MAP ranging from 30–45 mmHg despite receiving more than a liter of 5% albumin and titrated doses of vasopressors totaling more than 3000 mcg of phenylephrine, 20 mg of ephedrine, 180 mcg of epinephrine and 30 mcg of norepinephrine. Despite the low BP values, the patient maintained a palpable carotid pulse. The aorta was cannulated with an 18-gauge catheter for pressure transduction, which confirmed hypotension with a MAP of 35–45 mmHg. According to arterial waveform analysis, the patient maintained a supraphysiologic cardiac output and very low SVR consistent with vasoplegia. Transesophageal echocardiography demonstrated a hyperdynamic left ventricle but was otherwise normal (Figure 1).

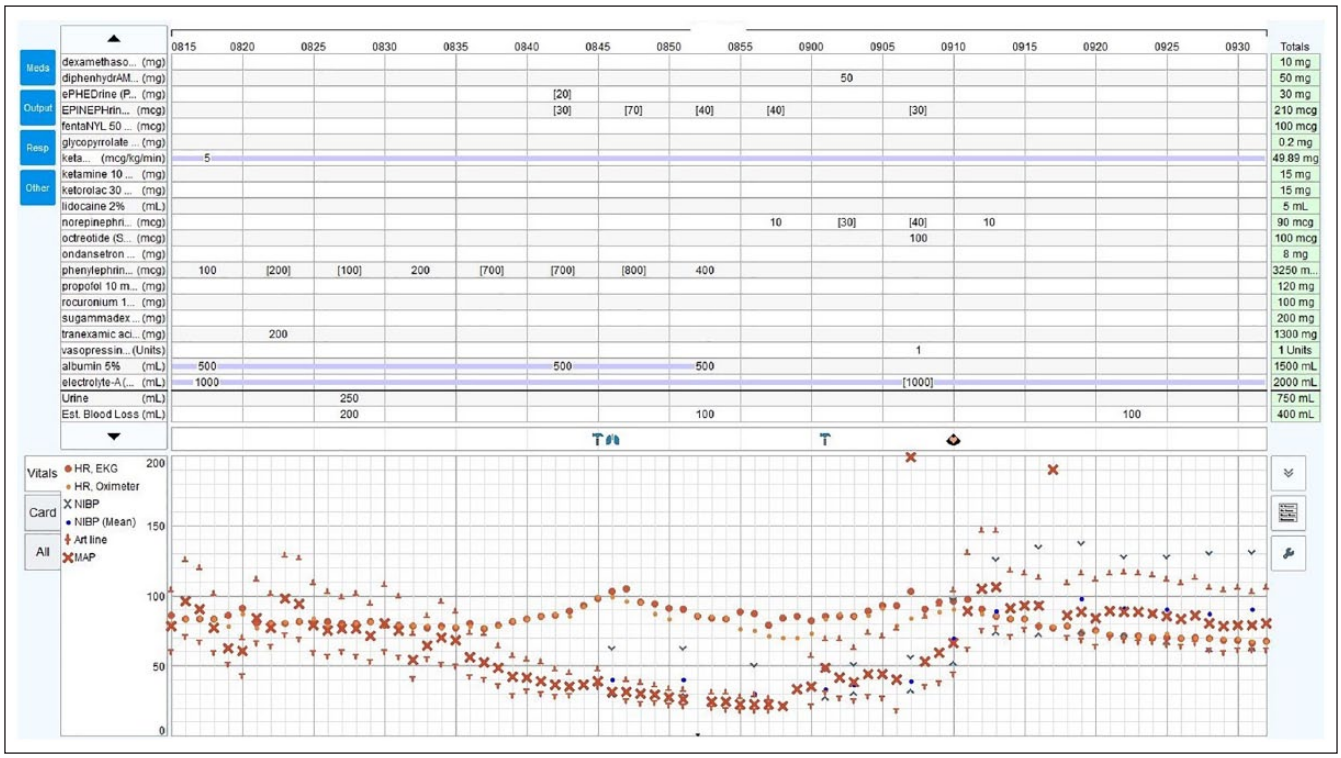

Figure 1. A copy of the electronic intraoperative record for focused on the period of thymoma resection and refractory hypotension.

Significant improvement in the patient's condition was observed only after the administration of octreotide 100 mcg and diphenhydramine 50 mg, improving the MAP from 45 to 60 mmHg over a 10-min period. With the addition of vasopressin and norepinephrine, the MAP increased to 105 mmHg before settling at 70–90 mmHg with no further hypotension for the remainder of the surgery. Following surgery, the patient had moderate sanguinous chest tube drainage accompanied with mild hypotension, managed expectantly with blood transfusion through postoperative day 1. The patient had an otherwise uneventful postoperative recovery, was discharged on postoperative day 4 and was doing well at 6-month follow-up.

Discussion

Somatostatin (SST) is an inhibitory peptide hormone that acts in the brain and the digestive system to regulate many different processes, including anterior pituitary secretion, smooth muscle contraction and splanchnic blood flow.[2,3] There are five SST G-protein-coupled receptor subtypes which regulate the activity of ion channels, enzymes and intracellular second messengers such as cyclic adenosine monophosphate (cAMP), inositol 1,4,5-trisphosphate, diacylglycerol and cyclic guanosine monophosphate (cGMP).[4] In the digestive system, SST suppresses the release of

numerous gastrointestinal hormones, including gastrin, secretin, motilin, vasoactive intestinal peptide, serotonin, insulin-like growth factor-1, glucagon and insulin. It decreases the rate of gastric emptying and but can increase phase 3 small bowel peristalsis.

As an analog of SST, octreotide binds to somatostatin receptor (SSTR) subtypes 2 and 5, which can be found in areas such as the brain, pituitary, and endocrine, exocrine pancreas and blood vessels.[5] In comparison to SST, octreotide has greater clinical utility because it is more potent, has a much longer half-life and is not associated with the rebound hypersecretion of hormones observed in SST.[5] The regulatory effects of octreotide have long been applied in the diagnosis and treatment of several cancers.[6] Perhaps, the most well-known indications for octreotide are in the treatment of acute variceal bleeding and carcinoid syndrome. The reduction of portal pressure from direct vasoconstriction of mesenteric arteries and portal-systemic collateral veins has been attributed to the inhibition of nitric oxide synthesis and release of glucagon. In cirrhotic patients, the administration of octreotide can partially correct the hyperdynamic circulation induced by peripheral vasodilation and can also facilitate the effects of vasoconstrictors independent of concurrent decreases in circulating nitric oxide and glucagon.[7–9] While the exact mechanism of increased peripheral arterial and venous tone is unclear, it appears that it may be primarily attributed to local vasoconstriction.[7,10,11]

Though possessing many similarities to octreotide, vasopressin is the more commonly used agent to increase arterial tone. Like SST, the G-protein coupled receptors of vasopressin can be found in many locations throughout the body. Specific to vasopressin, the activation of its receptors in vascular smooth muscle, the pituitary and renal collecting ducts result in arterial vasoconstriction, adrenocorticotropic (ACTH) release and increased renal reabsorption of water, respectively. This is in contrast with octreotide which can increase both venous and arterial tone. The hemodynamic effects of vasopressin and octreotide are substantially longer than adrenergic agonists, with respective half-lives of 24 and 100 min.[11,12] In the setting of acute variceal bleeding, the use of octreotide was found to be associated with lower rates of cardiovascular complications than vasopressin.[13] It can be reasonably inferred from these studies that octreotide is safe, being primarily associated with relatively minor side-effects including decreased gallbladder motility, nausea, diarrhea, steatorrhea and flatulence.[13]

Another agent that has been used in the setting of vasoplegia is the heterocyclic aromatic molecule methylene blue (MB).[14] MB has been found to improve MAP for patients following cardiac surgery, deep hypothermic circulatory arrest, protamine reaction and septic shock without apparent detrimental effect.[15,16] Octreotide and MB share many clinically significant characteristics. Both have relatively long durations of action; methylene blue has a terminal half-life of 5.25 h. Similar to octreotide, MB is an inhibitor of nitric oxide synthase and guanylate cyclase. Some research has suggested that like octreotide, the hemodynamic effects of MB may be more closely attributed to the more downstream cGMP pathway rather than inhibition of nitric oxide synthase.[17] The hemodynamic effects of both agents are most pronounced in the presence of certain conditions such as vasoplegia. In contrast, MB has very little hemodynamic effect when administered to nonvasoplegic patients.[18] It has also been shown to alleviate endothelial dysfunction and oxidative stress associated with diabetes mellitus in animal models.[19] Similar to octreotide, it appears that MB has the potential of doing more than simply increasing arterial tone; it was found to increase central venous pressure, pulmonary wedge pressure, cardiac output and SVR in patients with septic shock.[20]

In this case study, the patient developed refractory hypotension following tumor resection (Figure 1). Despite minimal surgical bleeding and aggressive fluid resuscitation, the patient remained profoundly hypotensive despite no apparent metabolic or anatomic derangements. Large amounts of adrenergic vasopressors were used with minimal efficacy. Observations from transesophageal echocardiography, direct visualization of the surgical field and aortic cannulation were consistent with the diagnosis of vasoplegia. The administration of both octreotide and diphenhydramine were temporally associated with their own incremental improvements in blood pressure. We deduced that both agents increased venous and arterial vascular tone based on improvements in cardiac filling, cardiac output and SVR. The patient also became much more responsive to subsequent vasopressor administration. The patient's response to octreotide and diphenhydramine suggests that the patient's vasoplegia and venous pooling may have been caused by the release of potent vasoactive substances from the thymoma, such as histamine, bradykinin, serotonin, prostaglandins, cytokines or other inflammatory mediators.

At our institution, intravenous octreotide has been commonly used as a means of decreasing surgical bleeding during hepatic resection and for the treatment of refractory hypotension. As with the use of all vasopressors, an effort should first be made to determine any underlying cause of hypotension. For instance, is the apparent hypovolemia a result of inadequate fluid administration or is it from venous dilation and splanchnic sequestration? Intraoperative events most commonly associated with vasoplegia and the subsequent administration of octreotide are bowel manipulation and neuroendocrine tumor mobilization. Octreotide appears to be most efficacious when given in the setting of splanchnic venodilation or low SVR. When given alone, octreotide appears to have a maximum effect on blood pressure that is much lower than adrenergic agents such as epinephrine. Any excessive effect on blood pressure can generally be attributable to the increased efficacy of concomitant vasopressors and therefore one may need to lower those dosages accordingly. Intravenous octreotide can be administered as a large bolus of 100–200 mcg or in a titrated fashion, given

in 20–40 mcg amounts until the desired blood pressure or plateau is achieved. The tachyphylaxis of octreotide may indicate a saturation of SSTR, at which time alternative causes of hypotension should be investigated.

It should be emphasized that octreotide has the potential to significantly reduce splanchnic blood flow. This may be advantageous in reducing surgical bleeding during hepatic resection but may also be deleterious on the perfusion of bowel or esophageal anastomoses. While octreotide appears to be well-tolerated, the lack of intraoperative studies means that it is not known how the safety and efficacy of octreotide compares with other treatments such as vasopressin and methylene blue.

Conclusion

Vasoplegia is a serious medical condition that can be life-threatening. Octreotide has the potential to dramatically normalize venous and arterial tone when other vasopressors are ineffective. To date, nearly all research on octreotide has focused on its endocrine and gastrointestinal effects. Further research is needed to determine the mechanism by which octreotide produces its hemodynamic effects. Intraoperative studies are needed to compare outcomes associated with the use of octreotide and other vasopressors. In particular, further research may clarify how octreotide can be used in conjunction with or instead of other non-adrenergic agents such as MB. We believe that this case report along with the evidence that is currently available demonstrates the potential clinical benefit of using octreotide as an adjunct with other vasopressors in the treatment of intraoperative vasoplegia.

Declaration of conflicting interests

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or small case series.

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Informed consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article. Documentation of conversation was also recorded in EMR.

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