CHEST Postgraduate Education Corner
CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

Octreotide

A Drug Often Used in the Critical Care Setting but Not Well Understood

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While the canonical function of somatostatin (SST) is to inhibit the secretion of growth hormone, it has a number of other physiologic effects that are less widely appreciated. Octreotide, an analog of SST, is not uncommonly used in the critical care setting, particularly for the treatment of variceal hemorrhage. Herein, we discuss the biology and pharmacology of SST, octreotide, and other SST analogs. We also review the evidence behind their use in esophageal variceal bleeds, hepatorenal syndrome, hypoglycemia due to sulfonylurea poisoning, and chylous pleural effusions.

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Abbreviations: cAMP = cyclic adenosine monophosphate; EVL = endoscopic variceal ligation; GFR = glomerular filtration rate; HRS = hepatorenal syndrome; SCr = serum creatinine; SST = somatostatin; SSTR = somatostatin receptor

Somatostatin (SST), also known as somatotropin release-inhibiting factor, was first isolated from the hypothalamus and found to inhibit the secretion of growth hormone and, to a lesser extent, thyroid-stimulating hormone and luteinizing hormone from the anterior pituitary. With precise identification of SST as 28- and 14-amino acid cyclic peptides (SST-28 and SST-14, respectively), SST analogs such as octreotide were synthesized.

Octreotide is not uncommonly used in the pulmonary and critical care setting, where it is used mainly in patients with suspected or known variceal hemorrhage, but also those with hepatorenal syndrome (HRS) and sulfonylurea-induced hypoglycemia. Other less common indications include treatment of chylous pleural effusions, hypertrophic osteoarthropathy,[1] and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia.[2] It has been our experience that clinicians are often unfamiliar with the pharmacology of octreotide, its mechanism of action, and rationale for its use. Our objective is to present a cogent analysis of the biology of SST and octreotide, with the goal of providing a clearer understanding of their use in disorders relevant to pulmonologists and intensivists. We will focus on (1) SST biology, (2) pharmacology of SST, octreotide, and other SST analogs, and (3) the use of these agents in esophageal variceal hemorrhage, HRS, hypoglycemia due to sulfonylurea toxicity, and chylous pleural effusions.

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SST Biology

SST is synthesized not only in the hypothalamus but also by δ cells of the pancreatic islets, the myenteric neural plexi, and the epithelial lining of the stomach and intestines. Based on the sites where it is found, it is not surprising that SST can influence numerous endocrine and exocrine functions of the GI tract and pancreas, including inhibition of the secretion of

insulin, glucagon, cholecystokinin, gastrin, secretin, serotonin, vasoactive intestinal peptide, motilin, and pancreatic polypeptide.[3,4] Thus, SST and its synthetic analogs are able to inhibit gastric acid production, gastric emptying, and GI motility, pancreatic exocrine and endocrine secretion, nutrient absorption (eg, glucose, fats, amino acids), and biliary flow and contractility. These functional effects of SST provide the rationale for the use of SST analogs in various GI and non-GI endocrine disorders such as carcinoid syndrome, islet cell tumors, β-islet cell hyperplasia (nesidioblastosis), and acromegaly.[4,5] In addition, SST and octreotide can induce vasoconstriction of the splanchnic vessels, thereby reducing blood flow in the splanchnic and portal venous systems.[3,4]

SST is first synthesized as a precursor molecule. The C-terminal end of prepro-SST (116 amino acids) is cleaved to form either SST-14 or SST-28, the latter consisting of an N-terminal region of 14 amino acids and a C-terminal segment composed of SST-14 (Fig 1).[6] The importance of distinguishing the two native SST isoforms is that they are differentially expressed in the body, resulting in distinct effects. For example, while SST-28 predominates in the small intestine and has a 10-fold greater potency in inhibiting insulin secretion as compared with SST-14, SST-14 is more effective at inhibiting glucagon release.[6]

Five distinct SST receptors (SSTRs) exist (ie, SSTRs 1-5).[6] SSTRs are G protein-coupled receptors widely distributed in the brain, exocrine and endocrine pancreas, GI tract, and splanchnic blood vessels. SST binds all SSTRs with high affinity, but octreotide is relatively specific for SSTRs 2, 3, and 5 (Table 1).[6-9] Binding of SST or octreotide to an SSTR activates the inhibitory G protein (Gi/o), which is bound to the cytoplasmic tail of the seven-transmembrane SSTR.

SST-mediated inhibition of hormone release occurs via several mechanisms (Fig 2): (1) activation of Gi/o by SST inhibits adenylyl cyclase, resulting in decreased intracellular cyclic adenosine monophosphate (cAMP) levels and attenuation of cAMP-mediated secretion of various hormones[10]; (2) engagement of SSTRs can inhibit voltage-gated calcium channels, resulting in the inhibition of calcium entry into the intracellular space, reduction in intracellular calcium, and inhibition of calcium-dependent hormone secretion; and (3) inhibition of protein kinase A and activation of phosphatases reduce phosphorylation of proteins required for transport and release of hormone-containing vesicles. SST-mediated splanchnic vasoconstriction occurs via at least two separate mechanisms (Fig 2): (1) inhibition of release of glucagon, a vasodilator, and (2) SSTR-3-mediated inhibition of endothelial nitric oxide synthase and of production of nitric oxide, also a potent splanchnic vasodilator. Interestingly, since cAMP is a transcriptional activator of the *SST* gene by binding to a cAMP response element, SST can downregulate its own expression.[4]

Pharmacology of SST, Octreotide, and Other SST Analogs

Clinical use of SST is limited by a very short circulating half-life (< 3 min) and, thus, SST administration is by continuous IV infusion; furthermore, rebound hypersecretion of affected hormones may occur after discontinuation or interruption of SST administration. By contrast, SST analogs have longer pharmacokinetic half-lives (eg, 1-2.5 h for octreotide) and can be administered subcutaneously as well as intravenously.[11] Octreotide is a cyclic peptide composed of eight amino acids (Fig 1), similar to the C-terminal ring of both SST-14 and 28. Most other SST analogs (eg, lanreotide, vapreotide) are also octapeptides, although pasireotide is a hexapeptide (Fig 1).

While the pharmacologic actions of octreotide and other SST analogs are generally similar to that of SST, differences in binding affinity to specific SSTRs create therapeutically relevant differences.[6] For example, compared with SST-14, octreotide exhibits 45-, 11-, and 1.3-fold more potent inhibition of growth hormone, glucagon, and insulin secretion, respectively.[6] Tachyphylaxis has been reported with continued octreotide use.[12]

Octreotide is available as octreotide acetate, an immediate-release form that requires daily subcutaneous or IV administration, and as octreotide long-acting release that can be administered intramuscularly once monthly.[12] Octreotide is mostly metabolized by the liver, although 30% to 35% of octreotide acetate is excreted in the urine as unchanged drug. Thus, octreotide accumulates in patients with moderate to severe renal or hepatic insufficiency.[13]

Octreotide and other SST analogs are generally well tolerated, particularly during short-term use (ie, < 1 month).[12,14,15] While most patients will experience adverse events related to octreotide therapy, these are usually mild and/or transient. Most adverse effects are GI and hepatobiliary in nature and are directly related to inhibition of the secretion of various hormones of the GI tract (Table 2).[12-18]

Lanreotide is available in the United States as a sustained-release depot formulation, administered once monthly as a deep subcutaneous injection for long-term administration.[19] Lanreotide is similar to octreotide in pharmacology, clinical actions, and most adverse effects. Vapreotide and pasireotide are also similar to octreotide in most respects, differing only in relative affinities for specific SSTRs.[15,20,21] These agents are not available in the United States at the time of writing, although pasireotide was recommended for approval by a Food and Drug Administration Advisory Committee in late 2012.[20,21]

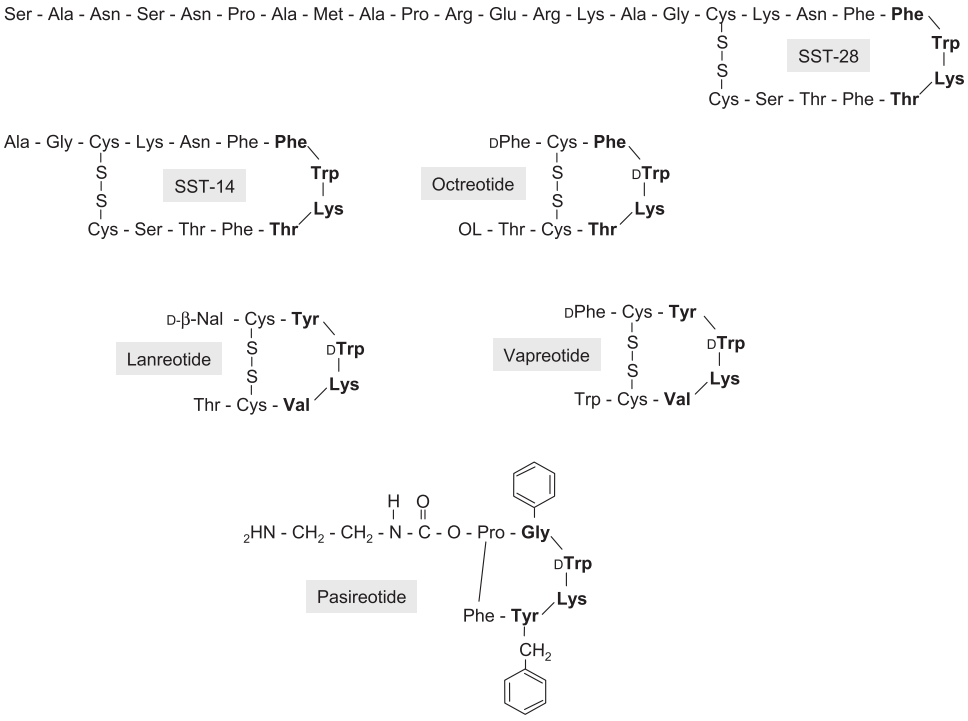

FIGURE 1. Amino acid sequence of somatostatin (SST)-14, SST-28, and SST analogs. The β turn in the SST-14 molecule, comprising the amino acids Phe[7], Trp[8], Lys[9], and Thr[10], is necessary for biologic activity. As demonstrated by the amino acid sequences of the SST analogs, residues Trp[8] and Lys[9] are essential for biologic activity, while Phe[7] and Thr[10] may undergo minor substitution. Lys = lysine; Phe = phenylalanine; Thr = threonine; Trp = tryptophan.

DISORDERS TREATED BY OCTREOTIDE

Variceal Hemorrhage

Esophageal and gastric varices are dilated venous collaterals that develop as a result of portal hypertension, most often from cirrhosis. The prevalence of varices correlates with severity of the liver disease and ranges from 40% in Child-Pugh A cirrhosis to 85% in Child-Pugh C cirrhosis.[22] Risk factors for bleeding include large varices and a hepatic venous pressure gradient > 12 mm Hg.[22] Medical and interventional prophylaxes such as nonselective β-blocker therapy and endoscopic variceal ligation (EVL) have decreased the incidence of initial bleeds from 30% to 40% to 15%[22,23] and of recurrent bleeding from 60% to 15%.[22] The 6-week mortality from each variceal bleeding episode is 15% to 20%, predominantly in patients with Child-Pugh C cirrhosis.[24] Factors associated with higher mortality are poor liver function (eg, higher Model for End-Stage Liver Disease score), severe portal hypertension, and failure to control bleeding (ie, continued bleeding or early rebleeding within 5 days of admission).[25] Initial management of variceal bleeding is similar to other forms of GI bleeding with a few caveats[22,24,26]: (1) avoid excessive volume expansion to avert further increases in portal hypertension, (2) reserve fresh frozen plasma for cases of continued bleeding to minimize the risk for transfusion-related acute lung injury,[27] and (3) treat prophylactically with ceftriaxone or a fluoroquinolone to improve outcome and mortality.[28,29]

Table 1—*Relative SSTR Subtype Selectivity Types of SSTR*[6-8]

SSTR[a]	Relative Binding by Octreotide	Examples of Effects Upon Binding by SST or Analogs
SSTR-1	…	Inhibits insulin secretion
SSTR-2	+++++	Inhibits glucagon, GH, TSH, and gastric acid secretion
SSTR-3	+++	Inhibits eNOS activity
SSTR-4	…	Suppresses voltage-gated calcium channels, reducing intracellular calcium
SSTR-5	++++	Inhibits insulin, GH, and TSH secretion

eNOS = endothelial nitric oxide synthase; GH = growth hormone; SST = somatostatin; SSTR = somatostatin receptor; TSH = thyroid-stimulating hormone.

[a] In rats, splanchnic blood vessels contain SSTRs 1-4.[9]

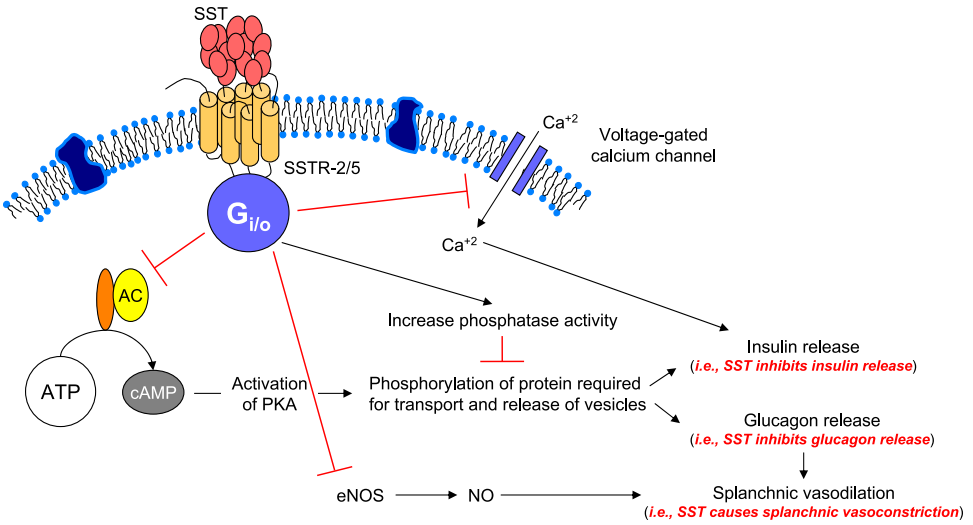

FIGURE 2. Simplified diagram of the key signaling events that occur after binding of SST or octreotide to the SSTR accounting for the major biologic effects of SST and its analogs (see text for discussion). AC = adenylyl cyclase; ATP = adenosine triphosphate; Ca^{2+} = calcium ion; cAMP = cyclic adenosine monophosphate; eNOS = endothelial nitric oxide synthase; $G_{i/o}$ = inhibitory G protein; NO = nitric oxide; PKA = protein kinase A; SSTR = somatostatin receptor. See Figure 1 legend for expansion of other abbreviation.

It seems intuitive that reduction of portal pressure by reducing splanchnic blood flow would be salubrious in acute variceal bleeding. Octreotide induces splanchnic vasoconstriction by inhibiting both nitric oxide synthesis and release of glucagon[30] (Fig 2). Octreotide blunts postprandial splanchnic hyperemia and this physiologic effect is beneficial in variceal hemorrhage since blood in the GI tract has the same stimulatory effect on blood flow as food.[31]

While results have been mixed in regard to the efficacy of octreotide in acute variceal hemorrhage, it appears to be most useful as an adjunct to endoscopic therapy, particularly when EVL is used instead of sclerotherapy.[22,32,33] In a randomized, placebo-controlled trial comparing sclerotherapy alone vs sclerotherapy plus octreotide infusion for 48 h in acute variceal hemorrhage, there were no differences in mortality, rebleeding, blood transfusion, or need for ICU admission.[34] However, since EVL has been shown to be superior to sclerotherapy,[22,24,35] these findings may not be as applicable, as EVL is now favored over sclerotherapy. A Cochrane meta-analysis suggested modest benefits from octreotide, namely, a reduction in RBC transfusion by one-half unit.[36] However, the studies included in this meta-analysis also had high numbers of patients treated with sclerotherapy.[36] A Cochrane review found that emergency sclerotherapy was comparable to vasoactive drugs alone (including 10 trials with octreotide).[37] Another meta-analysis showed that the use of splanchnic vasoconstrictors (SST, octreotide,

Table 2—*Adverse Effects of Octreotide*[12-18]

Adverse Effects	Percentage or Frequency of Occurrence of Adverse Effects
GI tract	
Diarrhea	≤ 80% with short-term use (< 1 mo)
Nausea, vomiting, anorexia, flatulence, steatorrhea, constipation, abdominal pain	≤ 15% with short-term use, 35%-50% with chronic use
Gallbladder and biliary tree	
Inhibits gallbladder contractility and bile secretion resulting in sludging with or without gallstone formation	< 2% with short-term use, ≤ 60% chronically
Acute cholecystitis, ascending cholangitis, biliary obstruction, cholestatic hepatitis, pancreatitis	Infrequently reported
Glucose homeostasis	
Hyperglycemia (due to inhibition of insulin release)	2%-8% with short-term use, ≤ 16% chronically
Hypoglycemia (due to inhibition of glucagon release)	Infrequent
Other	
Headache, alopecia, epistaxis, dizziness, fatigue, influenza-like symptoms, hypertension, anemia possibly related to vitamin B_{12} malabsorption (chronic use only), hypothyroidism due to inhibition of TSH release (chronic use only)	Infrequent

See Table 1 legend for expansion of abbreviation.

vapreotide, vasopressin, or terlipressin) was associated with significantly lower risk of acute all-cause mortality and transfusion requirements, and improved bleeding control; in studies that compared (1) terlipressin with SST, (2) terlipressin with vasopressin, (3) octreotide with terlipressin, (4) octreotide with SST, (5) octreotide with vasopressin, and (6) vasopressin with SST, there were no significant differences in efficacy.[38] A study of 100 patients with acute variceal bleeding treated with EVL demonstrated that prior treatment with octreotide significantly reduced the early rebleeding rate from 38% to 9% with a trend toward improved 30-day mortality.[33]

Despite limited but promising evidence that octreotide is beneficial for acute variceal hemorrhage, it is currently recommended that in suspected variceal hemorrhage, IV octreotide should be started as soon as possible before endoscopic therapy (Table 3), and be maintained for 2 to 5 days if variceal bleeding is confirmed.[22] This recommendation is due, in no small part, to the fact that octreotide and vapreotide are as effective as, but have a better safety profile than, the vasopressin analogs.[46,47]

Vapreotide reduces splanchnic blood flow and portal pressure in animal models.[48] In humans, vapreotide increases hemostasis of variceal hemorrhage before endoscopy and, when combined with either EVL or sclerotherapy, improves bleeding control, decreases early rebleeding, and increases short-term survival.[39,48,49]

In summary, the greatest therapeutic effect of octreotide and vapreotide in acute variceal hemorrhage appears to be the acute control of bleeding to enable use of EVL and a reduction in rebleeding rate after endoscopic therapy; unfortunately, there is little impact of these agents on long-term mortality, reflecting the poor prognosis associated with severe end-stage liver disease.

Hepatorenal Syndrome

HRS is a functional renal failure occurring in patients with advanced cirrhosis.[50] Type 1 HRS is a rapidly progressive form characterized by a doubling in serum creatinine (SCr) level or a 50% reduction in creatinine clearance within a period of <2 weeks; in type 2 HRS, deterioration of renal function progresses more slowly.[51] Type 1 HRS is associated with a 30-day mortality rate of up to 95% with a median survival time often <2 weeks, whereas the median survival is up to 6 months for type 2 HRS.[50,52]

The pathogenesis of HRS is considered to arise from splanchnic arterial vasodilation due to cirrhosis-induced production of nitric oxide, resulting in decreased effective circulatory volume. In response to this redistribution of blood volume, there is robust and sustained activation of the renin-angiotensin-aldosterone system, arginine vasopressin, and sympathetic axis, leading to renal vasoconstriction and renal insufficiency.[52,53] The splanchnic circulation escapes the effect of these endogenous vasoconstrictors because of the greatly increased local production of nitric oxide. Circulatory dysfunction with reduced cardiac output may also play a role in the response to compensatory mechanisms and progression to HRS.[52,54] Precipitating factors for HRS include large-volume paracentesis without volume expansion with albumin, spontaneous bacterial peritonitis and other systemic bacterial infections, GI bleeding and other causes of hypovolemia, and use of prostaglandin inhibitors (ie, non-steroidal anti-inflammatory drugs). However, although these conditions can precipitate HRS, it is important to rule out other forms of intrinsic renal failure (eg, acute tubular necrosis, acute interstitial nephritis) as well as prerenal azotemia (by its response to adequate fluid resuscitation) before making a diagnosis of HRS.

Liver transplant is the treatment of choice for HRS. A transjugular intrahepatic portosystemic shunt, volume expansion with albumin, and pharmacologic-induced splanchnic vasoconstriction provide additional treatment options in patients who are not transplant candidates or who require a bridge to transplantation.[55] Pharmacologic vasoconstriction of the splanchnic vascular beds is believed to reverse HRS by increasing effective arterial blood volume, thereby suppressing activation of the renin-angiotensin-aldosterone system and sympathetic nervous system, reversing

Table 3—*Recommended Dosages for Octreotide*[a]

Condition	Octreotide Dosage, Frequency, and Route	Comments
Esophageal variceal hemorrhage	50 μg IV bolus, then 50 μg/h IV for 2-5 d	Vapreotide dosing is identical to octreotide[39]
Hepatorenal syndrome	100-200 μg SC tid	Should be combined with midodrine 7.5-12.5 mg po tid and albumin IV
Hypoglycemia due to sulfonylurea poisoning	Adults: 50 μg SC or IV initial dose, then 50 μg SC or IV q6h for 3 doses Children: 1-1.5 μg/kg SC or IV, then 2-3 more doses q6h	Anecdotally, a wide range of doses and schedules have been reported.[40,41] Dose listed is based on a recent review.[42]
Chylous pleural effusion	Adults: 50 μg SC tid[43] Infants and children: 1-10 μg/kg/h IV infusion[44,45]	Based on anecdotal case reports

SC = subcutaneously.
[a] Unless specified, dosages are for adults.

compensatory renal vasoconstriction, and increasing renal perfusion.

Despite the presence of increased endogenous arginine vasopressin in HRS, vasopressin analogs, particularly terlipressin, along with albumin as adjunctive therapy, have emerged as the preferred pharmacologic therapy for HRS. Because SST and its analogs can constrict the splanchnic vessels, the use of octreotide has been investigated for the treatment of HRS. However, the vasoconstrictive effects of SST may be blunted in patients with cirrhosis, likely due to the antagonistic effects of local nitric oxide production.[14,56]

Based on retrospective[57,58] or prospective, double-blind, placebo-controlled studies,[59,60] octreotide monotherapy does not appear to be beneficial in HRS. Octreotide has been more widely evaluated in combination with other vasoconstrictor agents such as vasopressin and midodrine. Therapy with vasopressin, either alone or in combination with octreotide, was an independent predictor of renal function recovery; however, octreotide monotherapy was not associated with any statistically significant benefits[55,58]

Midodrine is an orally administered α_1-adrenergic agonist that causes vasoconstriction by contraction of the vascular smooth muscle. In patients with cirrhosis but without HRS, midodrine was demonstrated to increase mean arterial pressure, glomerular filtration rate (GFR), and urinary sodium excretion, while also decreasing plasma renin activity, and aldosterone and nitric oxide levels. However, in patients with HRS, midodrine's hemodynamic and renal effects were not as profound and there were no significant improvements.[61] The addition of octreotide to midodrine in nonazotemic patients with cirrhosis and ascites did, however, produce improvements in renal vascular resistance, renal blood flow, and GFR.[59]

Several studies have evaluated the clinical benefits of midodrine plus octreotide in the treatment of type 1 HRS[62-65]; unfortunately, none of these were randomized controlled trials. Two retrospective studies investigated the combination of midodrine with octreotide in HRS.[63,64] In one of these studies, patients treated with midodrine and octreotide, titrated to achieve an increased mean arterial pressure $\geq$ 15 mm Hg, had significantly lower 30-day mortality (43%) compared with control subjects (71%). In addition, patients treated with both midodrine and octreotide had significantly greater rates of reduction in SCr level (40%) than control subjects (10%).[63] In another study, patients treated with midodrine, octreotide, and albumin had significantly longer transplant-free survival (median, 101 days vs 18 days) and greater improvement in GFR (48 mL/min vs 34 mL/min) than untreated subjects; moreover, following multivariate analysis, treatment with midodrine and octreotide was independently associated with improved survival.[64] A prospective pilot study of five patients titrated midodrine (7.5-12.5 mg orally tid) and octreotide (100-200 μg subcutaneously tid) to achieve an increase in mean arterial pressure of $\geq$ 15 mm Hg.[62] Patients also received albumin 20 to 40 g/d titrated to maintain adequate central venous pressure. Patients receiving midodrine plus octreotide had substantial improvements in renal blood flow, GFR, SCr level, and urinary sodium excretion.[62] Compared with eight other patients receiving dopamine plus albumin, the 1-month survival in the patients treated with midodrine plus octreotide was significantly higher with 100% survival over the 20 days of treatment, compared with only 12% survival in dopamine-treated patients.[62] In a second prospective study, 14 patients received midodrine, IV octreotide, and IV albumin for an average of 14 days.[65] Significant improvements in renal function were reported in 10 of 14 patients (71%); four patients improved enough to undergo transjugular intrahepatic portosystemic shunt procedures and three underwent liver transplant.[65]

In summary, octreotide monotherapy does not appear to have significant benefits in the treatment of HRS. However, octreotide combined with another splanchnic vasoconstrictor like midodrine, often in conjunction with albumin (Table 3), show promise in improving renal function and increasing survival. It is presently unclear whether octreotide-containing combination regimens provide any additional benefit over use of pure vasoconstrictors alone. Well-designed randomized, prospective trials are needed to more clearly define the role of octreotide in HRS, but its use in combination regimens may be considered. One advantage of the octreotide plus midodrine regimen is that it can be easily administered to outpatients.

Hypoglycemia Due to Sulfonylurea or Quinine Toxicity

The sulfonylureas are frequently prescribed to treat type 2 diabetes mellitus. However, they have a high potential for overdose and toxicity, manifested by hypoglycemia that may occur several hours after drug intake. Hypoglycemia-induced secretion of counterregulatory hormones and activation of the sympathetic nervous system causes many of the glycopenic symptoms such as sweating, anxiety, nausea, and palpitations. With more profound hypoglycemia, patients may also experience dizziness, headache, visual disturbances, drowsiness, confusion, coma, or seizures.

Conventional management of sulfonylurea-induced hypoglycemia is administration of oral glucose and/or intermittent or continuous IV glucose.[66] While timely administration of glucose is imperative, it may also paradoxically lead to recurrent hypoglycemia, as the glucose load induces an insulin surge from the pancreas. Thus, initial therapy with IV glucose may not be

sufficient to counteract the hyperinsulinemic state induced by sulfonylurea toxicity.

Therapy with octreotide is now favored over glucagon and diazoxide to counteract hypoglycemia due to increased adverse effects associated with the latter two agents (Table 3).[42,67,68] A randomized, double-blind, placebo-controlled study of 40 patients compared standard treatment of sulfonylurea-induced hypoglycemia (50% IV glucose and oral carbohydrates) to standard treatment combined with one dose of 75 μg octreotide given subcutaneously.[68] Serum glucose values 4 to 8 h after initiating treatment were significantly higher and recurrent hypoglycemia was less frequent for patients receiving octreotide.[68] A recent comprehensive analysis of the literature concluded that octreotide should be considered first-line therapy for hypoglycemia caused by sulfonylurea poisoning.[42] Octreotide has also been shown to be efficacious in quinine-induced hyperinsulinemia and hypoglycemia.[69]

There appear to be several mechanisms by which octreotide inhibits insulin secretion. Octreotide binds to SSTR-5 present on pancreatic β islet cells, inhibiting the formation of cAMP and reducing influx of calcium into the cytoplasm, thus, preventing insulin secretion (Fig 2). Another mechanism of octreotide is inhibition of direct phosphorylation of specific proteins required for secretion of insulin-containing vesicles (Fig 2).

Chylous Pleural Effusion

Chylous pleural effusions are defined by the presence of a pleural-fluid triglyceride level > 110 mg/dL (in the nonfasting state) or of chylomicrons in the pleural fluid. Chylous pleural effusions are most commonly due to the disruption or obstruction of the thoracic duct, which may be further classified as traumatic or nontraumatic. Traumatic etiologies may be noniatrogenic (eg, deceleration injury, penetrating injuries, spine fracture or dislocation, and childbirth) or iatrogenic, the latter mostly following cardiothoracic surgery. The most common cause of nontraumatic chylothorax are malignancies, especially lymphoma, chronic lymphocytic leukemia, and metastatic cancer.[70] Due to the loss of immunoglubulins, lymphocytes, protein, and fat-soluble vitamins from the circulation, complications of chylous effusions include immunodeficiency, intravascular hypovolemia, decreased oncotic pressure, and malnutrition.

Management of chylous effusion primarily consists of treating the underlying disorder, maintaining adequate nutrition, and minimizing chyle production. Symptomatic effusions require large-volume thoracentesis or placement of a thoracostomy tube, but these measures do not prevent the reaccumulation of the chylous fluid; other treatment options include chemical pleurodesis and pleuroperitoneal shunts. Patients in whom conservative management fails are candidates for surgical management,[71] which includes thoracic duct cannulation and embolization or thoracic duct ligation.

Minimizing the accumulation of chyle would be an advancement in treatment since repeated removal of chylous effusion or surgical management of the thoracic duct are associated with significant morbidity. SST or octreotide reduces intestinal chyle production by inhibiting gastric, pancreatic, and biliary secretions, thus, decreasing chyle flow in the thoracic duct and providing a greater chance for healing.[72] One study demonstrated the presence of high affinity SSTRs in smooth-muscle cells of the human thoracic duct, suggesting the possibility of an additional, direct effect of SST on thoracic duct contraction.[73] Varying degrees of success have been observed with the use of SST and octreotide for chylous effusions associated with cancer or after tumor resection,[43] chylothorax after pediatric cardiothoracic surgery,[44,74] and congenital idiopathic chylothorax.[45] In general, these case reports described volume reduction of chylous effusions in patients treated with octreotide, resulting in greater symptomatic relief. Although prospective, comparative studies are lacking, octreotide may prove to be a reasonably effective and safe treatment option for chylous effusions (Table 3). By the same mechanisms, adjunctive octreotide may also provide therapeutic benefit for chylous ascites.[75]

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