# Octreotide: A Versatile Therapeutic Agent

Module 1

## Octreotide: A Multifaceted Therapeutic Tool

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# Octreotide: A Synthetic Analogue of Somatostatin

## Introduction to Somatostatin

Somatostatin, first identified in 1968, emerged from studies focused on the distribution of growth hormone-releasing factors. Researchers simultaneously discovered a substance in pigeon pancreatic extracts that inhibited insulin release, leading to the isolation and sequencing of somatostatin. Initially classified as a 14-amino-acid peptide, known as somatostatin-14, further research revealed the existence of a 28-amino-acid form and larger prohormonal structures.

### Distribution and Functions

The somatostatin family is widely distributed throughout the body, appearing in both neuronal and non-neuronal cells across various organ systems. Immunoreactive somatostatin is found in the hypothalamus, cerebral cortex, brain stem, spinal cord, and within sensory and gastrointestinal neurons. Key tissue sites include pancreatic islet delta cells, gastric and intestinal epithelium, salivary glands, and parafollicular cells of the thyroid.

Somatostatin functions as a circulating hormone, a paracrine agent, or a neurocrine agent, with predominantly inhibitory effects on various physiological processes. In the anterior pituitary, it inhibits the release of growth hormone (GH) and thyrotropin. In the pancreas, it suppresses the secretion of insulin and glucagon. Additionally, somatostatin inhibits the release of gut hormones such as gastrin, secretin, and vasoactive intestinal peptide (VIP). Its broad spectrum of effects also includes decreasing splanchnic blood flow, reducing intestinal motility, inhibiting gastric acid and pepsin secretion, lowering carbohydrate absorption, and enhancing water and electrolyte absorption from the large bowel.

### Clinical Applications and Limitations of Somatostatin

Due to its wide-ranging physiological actions, somatostatin has been explored as a therapeutic agent for various conditions. Clinical studies have shown that somatostatin administration can inhibit peptide secretions and provide rapid symptomatic relief in patients with acromegaly, insulinomas, glucagonomas, carcinoid tumors, VIPomas, non-tumoral secretory diarrhea, and gastrointestinal bleeding.

However, clinical use of native somatostatin is hindered by several factors, including its extremely short half-life of two to three minutes, necessitating continuous intravenous infusion. Its non-organ-specific actions and the potential for rebound hypersecretion of GH and other hormones following the cessation of treatment further complicate its application.

## Introduction to Octreotide

Octreotide, a synthetic analogue of somatostatin, was developed in 1980 and began clinical trials in the U.S. in 1984. It exhibits similar actions to those of endogenous somatostatin, specifically inhibiting the secretion of growth hormone and various regulatory peptides in the gastroenteropancreatic system. Octreotide's longer half-life compared to native somatostatin allows for subcutaneous administration, making it more practical for clinical use.

### Therapeutic Uses

Octreotide is utilized to manage symptoms associated with gastrointestinal neuroendocrine tumors, acromegaly, and other hypersecretory disorders, including diarrheal conditions. Its effectiveness in controlling excessive hormone secretion has made it a crucial therapeutic agent in endocrinology and oncology.

While octreotide is effective in managing various conditions, it is not without side effects. Common adverse effects include suppression of gallbladder contractility and bile production. Prolonged maintenance therapy may lead to complications such as cholelithiasis, pancreatitis, and clinically apparent liver injury. Thus, careful monitoring and management are essential during treatment with octreotide.

### Mechanism of Action

Octreotide functions by acting on somatostatin receptors, which are coupled to phospholipase C via inhibitory G proteins. This interaction leads to vascular smooth muscle contraction. Specifically, the alpha and beta-gamma subunits of the G proteins inhibit adenyl cyclase while stimulating phospholipase C.

At the cellular level, octreotide, like somatostatin, promotes increased calcium entry through L-type calcium channels, facilitating calcium-induced calcium release from the sarcoplasmic reticulum in smooth muscle cells. This process activates myosin light-chain kinase through interaction with calcium-calmodulin, thereby initiating muscle contraction. Furthermore, the release of calcium from the sarcoplasmic reticulum is enhanced by the formation of 1,4,5-inositol triphosphate, which is potentiated by phospholipase C.

Consequently, octreotide inhibits hormone release from the anterior pituitary gland, including thyroid-stimulating hormone and growth hormone, as well as hormones from the gastroenteropancreatic endocrine system, such as insulin and glucagon.

## Indications for Octreotide Use

Octreotide is primarily indicated for the treatment of acromegaly and thyrotrophinomas, as demonstrated in clinical studies. In patients with acromegaly, octreotide has shown greater clinical effectiveness than bromocriptine in several trials. For managing carcinoid syndrome, octreotide has proven more beneficial than current treatment options, particularly in cases of carcinoid crisis, where it has resulted in improved clinical outcomes.

Additionally, for patients with tumors that produce elevated levels of vasoactive intestinal peptide (VIP), such as VIPoma—especially in those with metastasized and refractory tumors—octreotide is often considered the drug of choice, as supported by clinical trials. Octreotide is also established as the first-line treatment for reducing stool or fistula output in patients experiencing high-output secretory diarrhea, such as those with cryptosporidiosis, particularly in individuals with AIDS or small intestinal fistulas.

While initial studies have shown positive outcomes for conditions such as hyperinsulinemia-induced neonatal hypoglycemia, insulin-dependent diabetes mellitus, reactive pancreatitis, dumping syndrome, and postprandial hypotension, further research is necessary to clarify and

confirm the utility of octreotide for these disorders before they can be integrated into treatment guidelines.

## Off-Label Uses

Octreotide is used off-label for conditions such as refractory or persistent diarrhea associated with chemotherapy, graft-versus-host disease, and AIDS-related diarrhea caused by cryptosporidiosis. It has also been utilized in the management of metastatic gastroenteropancreatic neuroendocrine tumors, advanced thymoma and other thymic malignancies, prevention of carcinoid crisis, hepatorenal syndrome, hypoglycemia due to sulfonylurea, congenital hyperinsulinism, ectopic Cushing syndrome, hypothalamic obesity, Zollinger-Ellison syndrome, dumping syndrome after gastrectomy, and small intestinal fistulas.

## Use of Octreotide in Pregnant and Lactating Patients

Octreotide is classified as a category B medication by the FDA, indicating that animal reproduction studies have not demonstrated identifiable fetal risk, though data from studies involving pregnant women remain insufficient and unclear. Limited studies on octreotide use during breastfeeding have shown significant concentrations of the drug in breast milk, comparable to serum levels. However, further research indicates that oral absorption of octreotide is not particularly effective.

## Use of Octreotide in the Pediatric Population

In pediatric patients, especially those under six years old, the safety and efficacy of octreotide have not been thoroughly established due to a lack of well-documented randomized controlled trials. Reports and clinical trials involving children, particularly those under two years, have noted serious adverse events, including hypoxia, necrotizing enterocolitis, and fatal outcomes. However, no definitive link between these adverse events and octreotide has been established, as many pediatric patients had significant comorbid conditions.

## Use of Octreotide in the Geriatric Population

Clinical studies involving octreotide have not adequately included participants aged 65 and older, making it difficult to assess the drug's response in the geriatric population compared to younger adults. Therefore, caution should be exercised during dose selection for older patients,

starting with lower doses and carefully titrating as needed, taking into account the higher prevalence of decreased cardiac, hepatic, and renal function, as well as other comorbidities and concurrent medications.

## Contraindications for Octreotide Use

The primary contraindication for octreotide is a hypersensitivity reaction to the drug or any of its components. Caution is also advised when administering octreotide to patients with insulinoma or type 2 diabetes mellitus who require intensive blood glucose monitoring and control, as the medication can significantly lower glucose levels and reduce insulin requirements by as much as 50%. Close monitoring of serum glucose concentrations is essential during octreotide therapy.

Additionally, octreotide can increase the bioavailability of bromocriptine by up to 40%. This is particularly relevant since both drugs are used in the treatment of acromegaly. Octreotide may also cause bradycardia, arrhythmias, or conduction defects, so it should be used with caution in patients who are at risk for these conditions.

## Clinical Pharmacology

Octreotide acetate functions similarly to somatostatin, acting as a potent inhibitor of growth hormone (GH), glucagon, and insulin. While somatostatin's inhibitory effects are widespread throughout the body, they are particularly significant within the endocrine and gastrointestinal systems. In the hypothalamus, somatostatin inhibits the secretion of thyroid-stimulating hormone, growth hormone, adrenocorticotropic hormone, and prolactin. It also suppresses the release of insulin, glucagon, gastrin, and various gastrointestinal peptides, leading to reduced splanchnic blood flow, decreased hepatic blood flow, and lowered gastrointestinal motility, while simultaneously increasing the absorption of water and electrolytes. Additionally, somatostatin acts as an inhibitory neurotransmitter and plays a role in inhibiting cell proliferation.

Octreotide is a synthetic octapeptide that shares a four-amino-acid similarity with native somatostatin, allowing it to exhibit pharmacological effects akin to those of somatostatin while overcoming some of its limitations. Unlike somatostatin, which requires continuous infusion, octreotide can be administered via subcutaneous injection or intravenous bolus. It has a significantly longer duration of action and is a more potent inhibitor of GH, glucagon, and insulin secretion. Preclinical studies indicate that octreotide is approximately 70 times more effective than somatostatin in inhibiting GH release, 23 times more effective in glucagon inhibition, and three times more effective in insulin inhibition.

### Somatostatin Receptors

Five subtypes of somatostatin receptors have been identified, known as sst1 through sst5, which function as G-protein-coupled receptors. Carcinoid tumors typically have a high concentration of type 2 receptors (sst2). Octreotide does not bind to receptor types sst1 and sst4, but it demonstrates high, low, and moderate affinity for types sst2, sst3, and sst5, respectively.

# Pharmacological Effects of Octreotide

## Pituitary Effects

Studies have shown that intravenous octreotide can profoundly suppress the GH response to insulin-induced hypoglycemia. It also significantly reduces thyrotropin release in response to thyrotropin-releasing hormone, with no notable effect on corticotropin or cortisol responses. In healthy individuals and acromegalic patients, subcutaneous octreotide has been found to induce significant reductions in GH release when stimulated by arginine. In controlled studies, octreotide administered subcutaneously demonstrated marked decreases in serum GH concentrations compared to saline-treated subjects.

## Gut-Peptide Effects

Similar to native somatostatin, octreotide effectively inhibits the release of peptides from the gastroenteropancreatic endocrine system. In clinical studies, twice-daily subcutaneous administration of octreotide to healthy male volunteers resulted in the suppression of postprandial insulin levels, particularly after breakfast and dinner, leading to mild transient hyperglycemia compared to saline-treated controls. Furthermore, glucagon levels were suppressed for up to six hours in those receiving octreotide. Research has also shown that doses of octreotide lead to dose-dependent suppression of various hormones, including gastrin, gastric inhibitory peptide, pancreatic polypeptide, secretin, neurotensin, and motilin.

**Table 1. Pharmacological Effects of Octreotide**

| SITE OR FUNCTION | EFFECT |
|---|---|
| Pituitary | inhibits growth hormone and thyrotropin secretion |
| Gut hormones | inhibits gastric acid, gastric inhibitory peptide, gastrin, motilin, neurotensin, secretin, vasoactive intestinal peptide |
| Pancreas | inhibits insulin, glucagon, pancreatic bicarbonate, pancreatic polypeptide |
| Intestinal motility | decreases |
| Blood flow to gut | decreases |
| Gut absorption | decreases carbohydrate absorption; increases water absorption and electrolyte absorption |

## Pharmacokinetics

Due to poor absorption from the gastrointestinal tract, octreotide is administered parenterally. It can be given as a subcutaneous bolus or intravenously for rapid action. After subcutaneous injection, octreotide is rapidly and completely absorbed, with peak concentrations of 5.2 ng/mL observed approximately 30 minutes after dosing. Studies indicate that intravenous and subcutaneous doses are bioequivalent, with peak concentrations and area under the curve values being dose-proportional for both routes of administration.

### Key Pharmacokinetic Characteristics

- **Distribution**: Rapid distribution from plasma (half-life of approximately 0.2 hours).
- **Onset of Action**: Approximately 30 minutes.
- **Volume of Distribution**: Estimated at 13.6 L.
- **Total Body Clearance**: Ranges from 7 to 10 L/h.
- **Time to Peak Plasma Concentration**: 30 minutes.
- **Binding**: Primarily to lipoprotein, with some binding to albumin.
- **Metabolism**: Hepatic metabolism.
- **Duration of Action**: Variable, extending from 8 to 12 hours depending on the type of tumor.
- **Elimination Half-Life**: Approximately 1.7 to 1.9 hours, compared to 1 to 3 minutes for the natural hormone.
- **Excretion**: About 32% of the administered dose is excreted unchanged in urine.

### Effects of Renal Impairment

The elimination of octreotide from plasma is prolonged in patients with renal impairment. In cases of mild renal impairment (creatinine clearance 40–60 mL/min), the half-life increases to 2.4 hours, and total body clearance drops to 8.8 L/h. In moderate impairment (creatinine clearance 10–39 mL/min), the half-life is approximately 3.0 hours with a total body clearance of 7.3 L/h. In severely impaired patients not requiring dialysis (creatinine clearance <10 mL/min), the half-life is about 3.1 hours, with total body clearance at 7.6 L/h. For patients with severe renal failure requiring dialysis, total body clearance is reduced to roughly half of that observed in healthy individuals (from about 10 to 4.5 L/h).

### Effects of Liver Cirrhosis

In patients with liver cirrhosis, the elimination of octreotide is also prolonged, with a half-life extending to 3.7 hours and total body clearance decreasing to 5.9 L/h. Patients with fatty liver disease may experience similar changes, with a half-life of 3.4 hours and total body clearance at 8.2 L/h.

## Forms of Octreotide

### Octreotide Acetate Injection

Octreotide Acetate Injection is available in the following forms:

- **Sterile 1-mL Ampules**:
    - Strengths: 50 mg, 100 mg, 500 mg
- **Sterile 5-mL Multidose Vials**:
    - Strengths: 200 mg/mL, 1000 mg/mL

### Octreotide Acetate Long-Acting Release

The long-acting release formulation of octreotide is an injectable suspension designed for depot use. This formulation has a relative bioavailability of 60% compared to subcutaneous octreotide and is administered in doses of 10 to 30 mg every four weeks. It is available in the following strengths:

- 10 mg per 6 mL
- 20 mg per 6 mL
- 30 mg per 6 mL

## Dosage and Administration

Octreotide can be administered either subcutaneously or intravenously, with subcutaneous injection being the preferred method for symptom management. To minimize discomfort with subcutaneous injections, it's advisable to use the smallest volume necessary to deliver the required dose. Avoid administering multiple injections at the same site in close succession; instead, rotate injection sites systematically.

Octreotide is not compatible with total parenteral nutrition solutions due to the formation of a glycosyl octreotide conjugate, which may reduce the drug's efficacy. However, it remains stable in sterile isotonic saline solutions or sterile 5% dextrose solutions for up to 24 hours.

For intravenous administration, octreotide may be diluted in volumes ranging from 50 to 200 mL and infused over 15 to 30 minutes, or it can be given as an IV push over three minutes. In emergency situations, such as a carcinoid crisis, a rapid bolus may be administered.

Dosage varies based on the specific indication, and it is generally recommended to titrate the dose according to the patient's response. The typical initial dosage is usually 50 mg, administered two or three times daily, with upward dose adjustments frequently necessary.

# Established Therapeutic Applications

## Acromegaly

Octreotide has been extensively studied in both U.S. and European trials for the treatment of acromegaly, a disorder caused by excess growth hormone (GH). In most patients with acromegaly, octreotide effectively suppresses GH secretion, leading to improvements in symptoms such as headaches and fatigue. In a study involving acromegalic patients, a single subcutaneous injection of 50 µg of octreotide reduced serum GH concentrations from an average of 30 ng/mL to 1.4 ng/mL within three hours. The goal of treatment is to lower GH levels to below 2 ng/mL. The maximum inhibition achieved was 95% of baseline levels, with GH remaining suppressed for up to nine hours. Notably, no hypersecretory rebound phenomena were observed, and the impact on insulin secretion was minimal and short-lived.

The acute effects of octreotide were also evaluated in a study involving 18 acromegalic patients, which showed a significant reduction in GH levels—approximately 80% decrease from an average of 36.4 µg/L to 7.4 µg/L within two to six hours post-administration. When comparing the effects of octreotide and bromocriptine on GH levels in 17 patients, octreotide demonstrated a more pronounced inhibitory effect. Plasma GH concentrations were at or below 5 µg/L in 10 of the 17 patients after octreotide administration, whereas bromocriptine achieved similar results in only 5 patients. In cases where patients did not respond to either drug alone, a combination therapy showed significant inhibition of GH release.

Long-term treatment (ranging from five to twelve months) with octreotide was explored in patients with resistant acromegaly—those unsuitable for surgery, radiation, or bromocriptine. Mean 24-hour GH levels decreased significantly with subcutaneous doses of 50 or 100 µg administered every 12 hours, particularly in patients with smaller pituitary tumors. Some patients required doses of up to 1500 µg daily to achieve maximum suppression of GH. Over the long term, somatomedin-C levels were normalized in four patients and improved in two others. Most subjects reported increased energy and well-being during treatment, and headaches often resolved within minutes of injection. Furthermore, some patients exhibited modest reductions in tumor size as assessed by computed tomography.

## Gastroenteropancreatic Tumors

Endocrine tumors of the gastroenteropancreatic (GEP) axis are rare, occurring in less than one percent of the population. These tumors are characterized by hypersecretion of regulatory gut peptides, leading to significant clinical symptoms, most notably severe, often life-threatening diarrhea. Treatment with octreotide aims to control pathological peptide hypersecretion and alleviate symptoms. While there are isolated reports of tumor regression associated with octreotide administration, data remain preliminary. Nevertheless, controlled trials and case reports suggest that octreotide plays a vital role in managing symptoms related to GEP tumors.

### Carcinoid Tumors

Carcinoid tumors are the most prevalent primary endocrine tumors of the gut, with serotonin being their primary secretory product. Patients typically experience symptoms such as severe flushing, sweating, bronchospasm, and diarrhea. A study on the long-term effects of octreotide in 25 patients with metastatic carcinoid tumors showed that self-administered octreotide (150 µg subcutaneously three times daily) effectively alleviated flushing and diarrhea in 88% of patients. Notably, 86% of these individuals experienced a greater than 50% reduction in episode frequency. Although some patients experienced a recurrence of symptoms after several months, urinary levels of 5-hydroxyindoleacetic acid (5-HIAA), a serotonin metabolite, decreased significantly in 96% of participants, with a median response duration exceeding 12 months.

### Gastrinomas

Gastrinomas, associated with Zollinger-Ellison syndrome, are characterized by excessive gastrin production, leading to heightened gastric acid secretion. A study showed that a single subcutaneous injection of 50 µg of octreotide significantly suppressed serum gastrin concentrations within the first hour, maintaining this suppression for up to 10 hours. There was also a notable decrease in gastric acid secretion, persisting for 18 hours, with no rebound effects observed.

### Insulinomas

Insulinomas are insulin-secreting tumors originating from pancreatic islet beta cells. In one case, a patient with a malignant insulinoma was treated with subcutaneous octreotide over 20

weeks, resulting in an increase in mean integrated 24-hour serum glucose levels from 83 to 222 mg/dL and a decrease in serum insulin from 796 to 356 µU/mL. Another report involved an 80-year-old patient with malignant insulinoma and severe hypoglycemia treated with octreotide for 30 weeks. After acute administration, serum glucose levels rose by 400%, while insulin levels dropped significantly. This improvement in serum glucose levels persisted, suggesting that octreotide may exert an effect on serum glucose that is independent of insulin suppression.

## Glucagonomas

Glucagonomas arise from pancreatic alpha cells and are known for secreting glucagon, leading to symptoms such as necrolytic migratory erythema, anemia, glossitis, and weight loss. Reports indicate that octreotide administration provides rapid symptomatic relief in patients with metastatic glucagonoma. In several cases, treatment resulted in the resolution of skin rashes within four weeks, although plasma glucagon levels initially suppressed returned to baseline within three to four months. Despite this increase in glucagon levels, clinical disease management remained satisfactory.

## VIPomas

VIPomas are tumors that secrete vasoactive intestinal polypeptide (VIP), resulting in large-volume secretory diarrhea, hypokalemia, metabolic acidosis, and gastric hypochlorhydria. In one case, a patient with severe secretory diarrhea associated with VIPoma syndrome was treated with octreotide, which effectively restored intestinal water absorption and reversed chloride secretion. Following an intravenous infusion, the patient’s plasma VIP levels decreased significantly, and subsequent long-term therapy with subcutaneous octreotide resulted in complete resolution of diarrhea over a nine-month period.

# Clinical Efficacy of Octreotide

## Octreotide in Acromegaly

Octreotide has demonstrated a strong and prolonged inhibitory effect on growth hormone (GH) secretion following single-dose subcutaneous administration in patients with acromegaly. Research indicates significant variability in the sensitivity of GH secretion to octreotide, with peak inhibitory effects occurring between 2 to 5 hours after administering a 50 µg dose. In one study, patients experienced an average GH suppression of 64% compared to placebo within the first 10 hours after receiving octreotide, with effects lasting more than 10 hours.

Further investigations comparing the effects of octreotide at doses of 50 µg and 100 µg confirmed that both doses produced a similar reduction in GH secretion within 2 to 6 hours. However, the higher dose (100 µg) resulted in significantly greater suppression from 2 to 10 hours. Additionally, plasma GH levels in 61% of patients fell within the normal range (less than 5 µg/L) after the 50 µg dose, and 78% of patients had levels below 10 µg/L.

In a single-blind placebo-controlled study, a dose-dependent effect of octreotide on GH inhibition was observed, with doses of 5 µg, 50 µg, and 500 µg leading to progressive increases in GH suppression. Notably, a 5 µg dose produced a 50% inhibition of GH secretion, while larger doses further enhanced this effect. The 50 µg dose resulted in a rapid decline in GH levels, noticeable within 15 minutes, achieving maximal suppression of 80% from baseline within 75 minutes. Importantly, no rebound hypersecretion was recorded once the suppressive effects subsided.

Studies comparing the GH-lowering effects of octreotide with those of oral bromocriptine at a dose of 2.5 mg revealed that octreotide produced a significantly greater reduction in GH levels. The maximal suppression achieved with octreotide was 82.8%, compared to 51.9% with bromocriptine. After treatment, normal plasma GH levels were observed in 71% of patients receiving octreotide versus 32% with bromocriptine. Additionally, GH levels remained suppressed for a longer duration following octreotide administration, with significant suppression lasting up to 10 hours, compared to 6 hours for bromocriptine. This suggests that octreotide and bromocriptine may act via different pathways to inhibit GH secretion, a notion supported by findings that GH-secreting tumor cells respond differently to both medications. Interestingly, while combining bromocriptine and octreotide did not enhance GH suppression

in most patients, significant inhibition was noted in two patients who were resistant to either drug alone.

## Octreotide in Carcinoid Syndrome

Carcinoid syndrome is characterized by elevated plasma serotonin levels and increased urinary excretion of its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), which serve as key indicators of disease activity. Short-term studies have demonstrated that octreotide can effectively reduce plasma serotonin levels. For instance, administering octreotide at a dose of 50 µg three times daily for three days resulted in a significant 30.9% reduction in whole blood serotonin levels in patients with carcinoid syndrome. Additionally, postprandial serotonin levels were also significantly lower following octreotide administration.

However, the effect of octreotide on urinary 5-HIAA excretion has shown variability across studies. Some researchers found no significant impact on 5-HIAA levels with subcutaneous octreotide, while others noted a small but significant reduction. In a noteworthy study, 150 µg of octreotide administered three times daily resulted in more than 50% reductions in 5-HIAA levels for 24 out of 25 patients with metastatic carcinoid tumors. Smaller doses tended to yield less pronounced effects on urinary 5-HIAA.

Moreover, octreotide administration has been associated with significant suppression of postprandial release of pancreatic polypeptide, gastric inhibitory peptide, and insulin. Preliminary reports indicate that a single dose of octreotide (50 µg) can also lead to a 50% reduction in circulating adrenocorticotropic hormone (ACTH) levels within four hours in patients with carcinoid-induced Cushing's syndrome.

In summary, octreotide has shown promising efficacy in both acromegaly and carcinoid syndrome, offering significant reductions in hormone levels and providing symptomatic relief for affected patients.

## Octreotide in VIPomas

Patients with VIPomas typically exhibit elevated plasma levels of vasoactive intestinal peptide (VIP) and pancreatic polypeptide, often leading to severe diarrhea and various metabolic disorders. Clinical studies consistently show that octreotide effectively reduces plasma VIP concentrations, though levels may still remain above the normal range. Research demonstrated that mean plasma concentrations of VIP, pancreatic polypeptide, neurotensin, and motilin

decreased progressively for 12 hours following an initial dose of octreotide. Specifically, after administering 100 µg of octreotide twice daily for one week, reductions were noted at 76%, 94%, 88%, and 70%, respectively, without any evidence of "escape" from the effects of the drug.

The effects of octreotide withdrawal on VIP secretion have yielded mixed results. Some studies reported rebound secretion for approximately 24 hours following drug withdrawal in patients with VIP-secreting tumors, while others indicated suppression of plasma VIP levels lasting three days post-withdrawal. In an intestinal perfusion study involving a VIP-secreting tumor patient, subcutaneous administration of 50 µg of octreotide increased fluid and electrolyte absorption in both the jejunum and ileum. This effect may result from a direct action of octreotide on intestinal fluid and electrolyte transport, or as a secondary response to decreased release of VIP and other peptides from the tumor mass. Furthermore, the rapid decrease in plasma VIP concentrations and reduction in diarrhea observed after administering 50 µg of octreotide three times daily suggest that the drug inhibits VIP release and/or secretion by the tumor. Interestingly, unlike normal volunteers, patients with VIP-producing tumors did not experience deterioration in glucose tolerance after octreotide administration, despite a complete inhibition of postprandial insulin secretion.

## Octreotide in Glucagonomas

Patients with glucagonomas often present with elevated plasma glucagon levels alongside symptoms such as necrolytic migratory erythema. Short-term studies have revealed that octreotide significantly decreases plasma glucagon concentrations. For example, one study reported a dramatic decline in baseline glucagon levels from 3780 to 1480 ng/L within 15 minutes after subcutaneous administration of 50 µg of octreotide twice daily. These levels remained suppressed (between 300 to 700 ng/L) for the entire 12 hours following the initial dose.

## Octreotide in Gastrinomas

Gastrinomas are characterized by elevated plasma gastrin levels, leading to gastric acid hypersecretion and related clinical symptoms such as peptic ulceration, diarrhea, and malabsorption. Numerous studies indicate that a single subcutaneous dose of octreotide, ranging from 50 to 200 µg, rapidly suppresses plasma gastrin levels and basal acid output,

usually normalizing these levels within 1 to 6 hours. In a study involving ten patients with gastrinomas, a single dose of 1 µg/kg of octreotide significantly reduced serum gastrin levels, achieving a mean maximum inhibition of 84% from baseline six hours post-administration. Three patients had their gastrin levels reduced to within the normal range.

The suppression of gastrin secretion began one hour after octreotide administration and lasted for 16 hours. In this context, no rebound gastrin secretion above baseline was observed in any of the patients during the 18-hour study period. However, some long-term studies reported severe rebound hypergastrinemia with up to a four-fold increase in serum gastrin levels 48 to 72 hours after discontinuing octreotide therapy. Additionally, significant reductions in gastric secretion and acid output were documented, with nearly complete inhibition occurring 3 to 4 hours after administration, leading to total neutralization of gastric secretion.

## Octreotide in Insulinomas

Insulinomas, the most common neuroendocrine tumors, are marked by excessive insulin release, causing recurrent symptomatic hypoglycemia. Multiple studies evaluating the effects of single-dose subcutaneous octreotide (50 or 100 µg) in patients with insulinomas have demonstrated a significant increase in plasma glucose levels within 60 to 90 minutes for most patients. Following the single dose, sustained improvements in hypoglycemia were observed for at least eight hours, accompanied by gradual reductions in plasma insulin and C-peptide concentrations, reaching their lowest levels approximately three hours after octreotide administration.

Interestingly, one study documented no suppression of plasma insulin levels in a specific patient, regardless of the octreotide dose administered. Despite this, mean plasma glucose levels were significantly higher after octreotide administration compared to control levels and those following native somatostatin. In two additional patients, a 50 µg dose of octreotide inhibited insulin levels to 40% of baseline values within 60 minutes, maintaining this suppression for over six hours without a rebound effect. This contrasts sharply with the dramatic rebound of insulin levels observed after discontinuing native somatostatin, which surged to 220% of baseline levels.

In summary, octreotide has proven to be an effective treatment for various neuroendocrine tumors, significantly impacting hormone levels and associated symptoms, thereby improving patient outcomes.

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