Therapeutic Reviews

Series Co-Editors: Andrew Wilcock, DM, FRCP, and Robert Twycross, DM, FRCP

Therapeutic Reviews aim to provide essential independent information for health professionals about drugs used in palliative and hospice care. The content is also available on www.palliativedrugs.com and will feature in future editions of the Hospice and Palliative Care Formulary USA and its British and Canadian counterparts. The series editors welcome feedback on the articles (hq@palliativedrugs.com).

Octreotide *AHFS 92:00*

Eva Murphy, MRPharm, Eric E. Prommer, MD, Mary Mihalyo, BS, PharmD, RPh, and Andrew Wilcock, DM, FRCP

University of Nottingham (E.M., A.W.), Nottingham, United Kingdom; Mayo Clinic Arizona (E.E.P.), Scottsdale, Arizona, USA; and Mylan School of Pharmacy (M.M.), Duquesne University, Pittsburgh, Pennsylvania, USA

Class: Synthetic hormone.

Indications: Symptoms associated with unresectable hormone-secreting tumors, e.g., carcinoid, VIPomas, glucagonomas and acromegaly; prevention of complications after elective pancreatic surgery;[1] †bleeding esophageal varices;[2] †salivary, pancreatic and enterocutaneous fistulas;[3,4] †intractable diarrhea related to high output ileostomies,[5,6] AIDS, radiation therapy, chemotherapy or bone marrow transplant;[3,7–10] †inoperable bowel obstruction in patients with cancer;[11,12] †hypertrophic pulmonary osteoarthopathy;[13] †ascites in cirrhosis and cancer;[14–16] †buccal fistula;[17] †death rattle; †bronchorrhea;[18] †reduction of tumor-related secretions.[14]

Pharmacology

Octreotide is a synthetic analog of somatostatin with a longer duration of action.[19] Somatostatin is an inhibitory hormone found throughout the body. In the hypothalamus, it inhibits the release of growth hormone, TSH, prolactin and ACTH. It inhibits the secretion of insulin, glucagon, gastrin and other peptides of the gastro-enteropancreatic system (i.e., peptide YY, neurotensin, VIP and substance P), reducing splanchnic blood flow, portal blood flow, GI motility, gastric, pancreatic and small bowel secretion, and increasing water and electrolyte absorption.[20] Somatostatin acts as an inhibitory neurotransmitter in the CNS and also inhibits cell proliferation.[21] In Type 1 diabetes mellitus, octreotide decreases insulin requirements. However, in Type 2 diabetes, octreotide suppresses both insulin and glucagon release, leaving plasma glucose concentrations either unchanged or slightly elevated.[22,23] Octreotide has a direct anticancer effect on solid tumors of the GI tract and prolongs survival.[24–27]

The inhibitory, antisecretory and absorptive effects of octreotide are utilized in a wide range of clinical settings:

Hormone-secreting tumors: Octreotide improves symptoms by inhibiting hormone secretion, for example:

- 5HT in carcinoid (improving flushing and diarrhea)
- VIP in VIPomas (improving diarrhea)
- glucagon in glucagonomas (improving rash and diarrhea)

Address correspondence to: Andrew Wilcock, DM, FRCP, Hayward House Macmillan Specialist Palliative Care Unit, Nottingham University Hospitals NHS Trust, Nottingham NG5 1PB, United Kingdom. E-mail: andrew.wilcock@nottingham.ac.uk

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Inoperable bowel obstruction in patients with cancer: Octreotide can provide rapid relief of nausea and vomiting. The optimal dose has not been formally identified, but reports suggest <50% of patients respond to the typical starting dose of 300 microgram/24 h,[28] and 75–90% respond to 600–800 microgram/24 h.[12,29] Although doses of up to 1500 microgram/24 h have been used,[30] a dose of 600–800 microgram/24 h is generally sufficient to identify those likely to respond.[29,31] In comparisons with scopolamine (hyoscine) *butylbromide* (60–80 mg/24 h; not USA), octreotide (300–800 microgram/24 h) provides more effective and rapid relief of nausea and vomiting and reduction in NG (nasogastric) tube output. However, in those patients responding to either drug, after about 4–6 days, overall symptom relief is similar, and NG tube removal possible with both.[29] (Although no head-to-head comparison has been published to date, it is likely that the same is true for glycopyrrolate (glycopyrronium).)

Ascites: Octreotide 300 microgram SC b.i.d. can suppress diuretic-induced activation of the renin-aldosterone-angiotensin system and its addition has improved renal function and Na^+ and water excretion in patients with cirrhosis and ascites receiving furosemide and spironolactone.[15] Octreotide is also reported to reduce the rate of formation of malignant ascites.[14,16] It may interfere with ascitic fluid formation through a reduction in splanchnic blood flow or as a result of a direct tumor antisecretory effect. Octreotide may also help improve the efficacy of diuretics as in cirrhosis.[32] Octreotide could be considered in patients with rapidly accumulating ascites requiring frequent paracentesis despite diuretic therapy. Octreotide may also help resolve chylous ascites and/or pleural effusion secondary to yellow nail syndrome,[33] ruptured thoracic duct,[34] cirrhosis,[35–37] peritoneal dialysis,[38] or cancer.[39]

Other antisecretory effects: Octreotide reduces salivary production and may be of use in salivary or buccal fistulas.[4,17] Experience of its use in death rattle is limited and recommended only in the context of a clinical trial.[40] The use of octreotide led to rapid and complete control of bronchorrhea (>1L/24 h) in a patient with diffuse adenocarcinoma of the lung.[18] A systematic review supports the prophylactic use of octreotide with pancreatic surgery *for cancer*, to reduce the risk of complications, e.g., leak, fistula, but not with pancreatic surgery for other reasons.[1] Octreotide is recommended first-line for chemotherapy or radiotherapy-induced diarrhea when severe (i.e., increase ≥7 stools/day over baseline, hospital admission and IV fluids >24 h required) and second-line for less severe diarrhea which does not respond to loperamide 16–24 mg/day.[9,10] For those who have experienced severe chemotherapy-induced diarrhea, prophylactic depot octreotide is recommended for subsequent cycles. Octreotide also has been used for the treatment of enterovesical fistula,[41] and to improve mucous discharge from rectal cancers.[14]

Pain: Octreotide is reported to have an analgesic effect in patients with cancer, e.g., in bone pain from metastatic carcinoid, in hypertrophic pulmonary osteoarthopathy, pain arising from GI cancer, or when given IT.[13,42–44] However, a small RCT found octreotide to be no better than placebo.[45] Octreotide also is reported to be of value in chronic nonmalignant pancreatic pain caused by hypertension in the scarred pancreatic ducts.[46,47] Benefit could be secondary to its antisecretory action;[48] suppressing exocrine function by administering pancreatin supplements also reduces pain in 50–75% of patients with chronic pancreatitis.[49]

Miscellaneous: At doses far below those necessary for an antisecretory effect (e.g., 1 microgram SC t.i.d.), octreotide protects the stomach from NSAID-related injury, probably via its ability to reduce NSAID-induced neutrophil adhesion to the microvasculature.[50] Somatostatin receptors have been identified on leukocytes and, in rats, octreotide has been shown to suppress inflammation.[51] A recent systematic review casts doubt on the value of octreotide in the management of bleeding esophageal varices.[2]

Octreotide is generally given as a SC bolus or by CSCI[52] but can be given IV when a rapid effect is required. Octreotide also has been administered IT (as an analgesic).[44] A long-acting depot formulation is also available but evaluation has been generally limited to hormone-secreting tumors.[53] Benefit from depot octreotide has been reported in a RCT for the prevention of chemotherapy-related diarrhea[7] and in cancer patients with bowel obstruction.[54,55] Lanreotide is an alternative sandostatin analog also available in normal and depot formulations.

Onset of action: 30 min.

Time to peak plasma concentration: 30 min SC.

Plasma half-life: 1.5 h SC.

Duration of action: 8 h.

Cautions

Serious drug interactions: Octreotide markedly reduces plasma cyclosporine concentrations and inadequate immunosuppression may result. Increase the cyclosporine dose by 50% before starting octreotide, and monitor the plasma concentration daily to guide further adjustments.[56]

Insulinoma (may potentiate hypoglycemia). In Type 1 diabetes mellitus, insulin requirements may be reduced by up to 50%; monitor plasma glucose concentrations to guide any dose reduction needed with insulin or oral hypoglycemic agents. Octreotide increases the bio-availability of bromocriptine by about 40% (consider when using the combination in acromegaly).[56]

Cirrhosis, renal failure requiring dialysis (both lead to reduced elimination which may necessitate a dose reduction). May cause gallstones (although the manufacturer advises ultrasound examination of the gallbladder before treatment and every 6–12 months thereafter, this is generally not necessary in palliative care). Avoid abrupt withdrawal of short-acting octreotide after long-term treatment (may precipitate biliary colic caused by gallstones/biliary sludge).

May cause bradycardia, conduction defects or arrhythmias; use with caution in at-risk patients. Monitor thyroid function during long-term treatment (may cause hypothyroidism).

Undesirable Effects

For full list, see manufacturer's PI.

Bolus SC injection is painful (but less if the vial is warmed to room temperature).

Dry mouth, flatulence (lowers esophageal sphincter tone), nausea, abdominal pain, diarrhea, steatorrhea (GI undesirable effects may be reduced by administering octreotide between meals or at bedtime), impaired glucose tolerance, hypoglycemia (shortly after starting treatment), persistent hyperglycemia (during long-term treatment), gallstones (10–20% of patients on long-term treatment), pancreatitis (associated with gallstones).

Dose and Use

Dose varies according to indication (Table 1). Some of the recommendations are based on experience with only a small number of patients, so the dose should always be titrated according to effect. Once improvement in the symptom is achieved, reduction to the lowest dose that maintains symptom control can be tried.

Extrapolation from t.i.d. dosing may explain why 300–600 microgram/24 h CSCI is a common recommendation. However, because a 1000 microgram/5 mL multidose vial is available, it is simpler to dose octreotide in multiples of 250 microgram instead, e.g., 250 microgram, 500 microgram, etc.

Octreotide can be painful if given as an SC bolus. This can be reduced if the ampule is warmed in the hand to body temperature before injection. To reduce the likelihood of inflammatory reactions at the skin injection site with CSCI, dilute to the largest volume possible (e.g. for a McKinley T-34 syringe pump, 22 mL in a 30 mL luerlock syringe given over 24 h) and consider the use of 0.9% saline.

There are 2-drug compatibility data for octreotide in 0.9% saline with diamorphine (not USA), haloperidol, scopolamine *butylbromide* (not USA), scopolamine *hydrobromide*, midazolam, morphine sulfate, ondansetron, and oxycodone (injection not USA). Incompatibility may occur with dexamethasone or levomepromazine.

More details and 3-drug compatibility data can be found on www.palliativedrugs.com Syringe Driver Survey Database. For compatibility data in water for injection, see Charts A4.1–A4.6 on the site.

Depot formulation: A depot formulation of octreotide 10–30 mg, given every 4 weeks is available (Sandotatin LAR®). This has a relative bioavailability of about 60% compared to SC octreotide. Generally, the depot formulation is used only when symptoms have first been controlled with SC octreotide. Patients who have not previously received SC octreotide should have a test dose of 50–100 microgram SC and, provided there are no unacceptable undesirable effects, then switched to the depot injection. The depot formulation requires deep IM injection into the gluteal muscle; to minimize irritation, use alternate sides for subsequent injections.

Table 1
Dose Recommendations for SC Octreotide

Indication	Starting Dose	Usual Maximum
Hormone-secreting tumors		
acromegaly	100–200 microgram t.i.d.	600 microgram/24 h[20]
carcinoid, VIPomas, glucagonomas	50 microgram once daily or b.i.d.; increased to 200 microgram t.i.d.	1500 microgram/24 h; rarely 6000 microgram/24 h[57]
Intractable diarrhea (including that caused by chemotherapy and radiotherapy)	300–450 microgram/24 h	1500 microgram/24 h,[9,10,58] occasionally higher
Intestinal obstruction	250–500 microgram/24 h	750 microgram/24 h, occasionally higher
Tumor-antisecretory effect	50–100 microgram b.i.d.	600 microgram/24 h[14]
Ascites	200–600 microgram/24 h	600 microgram/24 h[16]
Bronchorrhea	300–500 microgram/24 h[18]	
Hypertrophic pulmonary osteoarthopathy	100 microgram b.i.d.[13]	

In acromegaly, stop the SC dose of octreotide when the first depot injection is given; for other neuroendocrine tumors, continue the SC dose for a further 2 weeks.

In a recent survey, 40% of clinicians reported the use of depot formulations in the management of cancer-related bowel obstruction.[59] There is limited published experience of their use in this setting, although benefit in a small number of patients with ovarian cancer for up to 15 months has been reported.[55] A reduction in NG tube output and symptomatic benefit is evident within 24 h.[54]

Lanreotide

Patients with acromegaly can be started directly on the depot formulation. It is given by deep SC into the gluteal region:

- start with 90 mg every 4 weeks for the first 3 months (60 mg in moderate-severe hepatic or renal impairment
- if necessary, increase to 120 mg every 4 weeks

Supply

Octreotide

Sandostatin® (Novartis)

Injection 50 microgram/mL, 1 mL amp = $12; 100 microgram/mL, 1 mL amp = $23; 500 microgram/mL, 1 mL amp = $111; 1 mg/5 mL multidose vial = $1,172; 5 mg/5 mL multidose vial = $4,525; *for prolonged storage, keep unopened ampules and vials in a refrigerator; a multidose vial can be kept for up to 2 weeks at room temperature for day to day use.*

Octreotide (non-proprietary)

Injection 50 microgram/mL, net price 1 mL amp = $10; 100 microgram/mL, 1 mL amp = $13; 500 microgram/mL, 1 mL amp = $82; 1 mg/5 mL multidose vial = $238; 5 mg/5 mL multidose vial = $955; *for prolonged storage, keep unopened ampules and vials in a refrigerator; a multidose vial can be kept for up to 2 weeks at room temperature for day to day use.*

Sandostatin LAR® (Novartis)

Depot injection (microsphere powder for aqueous suspension) 10 mg vial = $1,968; 20 mg vial = $2312; 30 mg vial = $3,861 (all supplied with diluent and syringe), IM injection only, every 28 days; *for prolonged storage, keep in a refrigerator and protect from light; vial can be brought up to room temperature 30–60 min before required but must only be reconstituted immediately before injection; see instruction booklet provided with vial for recommended reconstitution technique.*

Lanreotide
Somatuline Autogel® (Beaufour Ipsen)
Depot injection (prefilled syringe) 60 mg = $2,209; 90 mg = $2,873; 120 mg = $4,318; *for prolonged storage, keep in a refrigerator and protect from light; the syringe should be brought up to room temperature 30 min before required but should only be removed from its packaging immediately before injection.*

Abbreviations/Key

†	Off-label indication
5HT	5-hydroxytryptamine, serotonin
ACTH	Adrenocorticotrophic hormone
CSCI	Continuous subcutaneous infusion
GI	Gastrointestinal
IT	Intrathecal
NG	Nasogastric
RCT	Randomized controlled trial
SC	Subcutaneous
TSH	Thyroid-stimulating hormone
VIP	Vasoactive intestinal peptide

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