Present role and future possibilities of octreotide treatment

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Somatostatin plays an important role in regulation of neurotransmission and secretion, prevents release of growth hormone, thyroid-stimulating hormone, pancreatic enzymes, gastrointestinal hormones. Somatostatin analogue, octreotide was the first formulation used in clinical practice with a rationale to inhibit secretion of neuropeptides secreted by gastrointestinal neuroendocrine tumour which express somatostatin receptors. Octreotide plays an important role in the treatment of neuroendocrine tumours, acromegaly, portal hypertension with variceal haemorrhage and different other rare conditions. This review focuses on the present role and clinical use of octreotide. New therapeutical possibilities are also discussed.

KEYWORDS: somatostatin, octreotide, gastropancreatic neuroendocrine tumours, chromogranin-A

Somatostatin (SSA), a tetradecapeptide inhibits the secretion and action of numerous peptide hormones, neurotransmitters, and regulates pituitary, pancreatic and gastrointestinal hormone secretion. SSA also controls cell proliferation in normal tissues and in tumours. SSA was discovered by *Brazeau and Guillemin* in 1973 (1, 2).

Somatostatin is rapidly degraded in human plasma (half-life 1 to 2 minutes) which limits its clinical use. Octreotide with a half-life of 100 minutes was the first biologically active somatostatin analogue, which was introduced in clinical practice in late 1980s (3). Somatostatin binds to its specific receptors (SSTR) expressed by the target tissues (3). Five receptors have been recognized, pancreatic islet cells express all five receptors, SSTR2 and 5 are expressed by pituitary tumours, endocrine pancreatic tumours and carcinoids express mainly SSTR2 (3).

Octreotide acetate, a cyclic octapeptide is a long-acting peptide with pharmacologic actions mimicking those of the natural hormone somatostatin.

Octreotide is an even more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. Octreotide also decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide (VIP), secretin, motilin, and pancreatic polypeptide (4).

The short-acting, immediate release (IR) octreotide formulation is given subcutaneously (sc.) or intravenously (iv.). The drug is absorbed rapidly and completely from the injection site. The elimination of octreotide from plasma had an apparent half-life of 1.7 to 1.9 hours compared to 1 to 3 minutes of the natural hormone. The duration of action of octreotide is variable, but extends up to 12 hours depending upon the type of the tumour. Elimination is prolonged in patients with renal and hepatic failure (4).

The long-acting formulation, the octreotide LAR which is based on microparticle and nanoparticle drug-delivery technologies was introduced in 1995 (3), is administered by monthly intramuscular (im.) injection.

Lanreotide (Somatulin) is another metabolically stable long-acting formulation, which has a different release pattern and the same binding profile (5).

Pasireotide (Signifor) is a next-generation multireceptor-targeted somatostatin analogue with high affinity for SSTR1-3 and 5 receptor, binding affinity to SSTR5 is 39-fold higher than that of octreotide (3), its use is restricted to those patients who do not respond to octreotide or lanreotide treatment.

Effects of SSA treatment

Antineoplastic effect

SSAs are used to treat tumour-related hormone hypersecretion by binding directly to tumour cells or inhibition of growth factors, angiogenesis and immune system (2). *Erikkson and Oberg* found tumour growth stabilization in 50% of patients with gastroenteropancreatic neuroendocrine tumours (GEP-NET) treated with octreotide, while tumour regression was observed in 10-20% of all patients (6). Octreotide also inhibits some angiogenic factors, thus could stop tumour growth indirectly, by inhibition of angiogenic factors, such as vascular endothelial growth factor (VEGF) (7).

Some studies support the antisecretive role of SSA, some patients with hypergastrinaemia and *Zollinger-Ellison syndrome* treated with octreotide showed a reduction in tumour growth and reduction of serum chromogranin A (CgA) levels (2, 7).

Octreotide acetate substantially reduces growth hormone (GH) and/or IGF-1 (insulin-like growth factor)-1 levels in endocrine and non-endocrine tumours. Octreotide acetate suppresses secretion of thyroid stimulating hormone (TSH).

Tolerability, side effects

Gastrointestinal side effects are mild to moderate, as bloating, abdominal discomfort, diarrhoea, stomach pain usually after the first few month related to disruption of GEP hormone signalling and reduced secretion of pancreatic enzymes (8).
Inhibited secretion of cholecystokinin leads to cholestasis, biliary sludge, gallstone formation, microlithiasis (8). Single doses of octreotide acetate have been shown to inhibit gallbladder contractility and to decrease bile secretion in normal volunteers.
Prolongation of QT interval on electrocardiogram have been shown is some patients treated with octreotide causing bradycardia (9), but patients with acromegaly also display ECG abnormalities without treatment. Severe complications as acute myocardial infarction have also been reported (3).
First generation somatostatin analogues cause impaired glucose tolerance, patients with diabetes mellitus are recommended to control their blood sugar level.
Other side effects: weakness, tiredness, itching, joint and bone pain, even bone fracture, headache, urinary tract infection, injection site haematoma, bruising, oedema, flushing and blurred vision.

Dosage and administration of octreotide

Initial therapy is octreotide IR for 3-7 days to test the tolerability of the drug before using long-acting formulation and keep using it for 14 days parallel until the LAR formulation reaches its effect. Initial dose of IR drug is 100-500 µg sc. two to four times daily (10). The dose must be increased until the control of symptoms is reached. The recommended dose of LAR form is 10 to 30 mg im. (maximum 60 mg) depending on the maximum dose of IR formulation, if needed the interval between administrations could be decrease.
The duration of treatment with octreotide LAR is lifelong if well-tolerated.
In cases of any operation or invasive procedures prevention of carcinoid crisis is important, a single dose of IR formulation (250–500 µg sc.) is recommended 1-2 hrs before procedure, while in octreotide naive patients 500 µg sc. must be used.

Follow-up examinations of octreotide therapy

The patient should be examined every 3 months CT/MRI should be made every 6 months. Annual OctreoScan (somatostatin receptor scintigraphy) is indicated if new symptoms occur. Tumour markers must be repeated every 3-6 months, for GEP-NET chromogranin A (CgA is co-released with peptide hormones, stored in tumour cells and release into circulation), 24-hour urine collection to determine 5-hydroxy indole acetic acid (5-HIAA), (serotonin is co-stored with CgA in secretory granules). For pancreatic NET the predominant peptide should be measured (10).
Regular check-up of blood glucose and TSH levels are also recommended.
Regular ECG analysis is needed to check QT interval. Abdominal ultrasound is also required to check gallstone formation, biliary sludge.

Clinical use of somatostatin analogues

Octreotide is the currently used treatment for gastroenteropancreatic neuroendocrine tumours, carcinoid tumours and acromegaly.

Gastroenteropancreatic neuroendocrine tumours (GEP-NET)

GEP-NET are rare tumours classified as foregut, midgut and hindgut neoplasms based on localization. These tumours could be well-differentiated, slow growing or poorly differentiated, malignant neoplasms (11). Non-functioning endocrine tumours do not secrete measurable amounts of hormones (30-50% of tumours), while active hormones secreted by functioning neoplasms contribute to different clinical symptoms, so called carcinoid syndrome. Symptoms of carcinoid syndrome are mild to severe diarrhoea, flushing of the face, wheezing attacks. Clinical symptoms of the tumours could lead to their early diagnosis, while clinically silent, non-functioning tumours are often diagnosed only when the metastasis are present (10).
Well-differentiated endocrine tumours of GEP are *Zollinger-Ellison syndrome* (gastrinoma), insulinoma, glucagonoma, VIP-secreting tumours (12). These tumours are often part of multiple endocrine neoplasia type I (MEN1) syndrome, diagnostic criteria of which include the presence of two or three endocrine tumours as pituitary, parathyroid and GEP tumours.
Gastric carcinoids (GC) represent 23% of all gastrointestinal neuroendocrine tumours (2, 13). The annual incidence is 0.2/100 000. The incidence of the gastric carcinoids have been increased in the past decades by 10 to 15-fold, while the 5-year survival rate increased from 50% to 63% (14).
Three types of gastric carcinoids are known: type I (GCs1) accounts for 75-80% of all GCs, usually they are well-differentiated, non-functioning, incidentally detected and frequently occurring in middle aged women, associated with chronic atrophic gastritis (2). GCs1 tumours originate from enterochromaffin-like (ECL) cells in response to hypergastrinaemia associated with chronic atrophic gastritis. These ECL cells expresses gastrin receptors mediating cell growth and stimulating acid secretion (15). Destruction of parietal cells in chronic gastritis leads to achlorhydria, which cause hypergastrinaemia leading to ECL cell hyperplasia and carcinoid development (16).
Type II GCs (GCs2) develops in patients with MEN1 and *Zollinger-Ellison syndrome*, related to hypergastrinaemia.

These tumours are small multiple polyps in the fundic mucosa. Their local excision is recommended. Type III GCs (GCs3) tumours are sporadic, solid, ulcerated malignancies with higher risk of metastatic spreading. Usually develops in older men, with signs of anaemia, weight loss, associated with bronchospasm, flushing.

Gastric carcinoids are usually treated conservatively, GCs1 with a diameter less than 10 mm must be annually followed by endoscopy, and endoscopic resection is recommended even in small tumours (17). Sometimes it is not easy because of multifocal or submucosal localization. Tumours showing deep invasion, or positive margin resection must be treated surgically (18).

Chemotherapy used in pancreatic NET is usually not working in gastrointestinal NET tumours. Based on the pathogenesis of these carcinoids somatostatin analogues have been used since 1980 to treat symptoms especially caused by VIPomas and gastric carcinoids due to their ability to express somatostatin receptors (2). Long-acting octreotide is used for functioning and non-functioning neuroendocrine tumours due to their ability to inhibit hormone release and neoplastic growth by binding to SSTR2- and SSTR5-receptor. Endocrine pancreatic and gastrointestinal carcinoid tumours can express different SSTR, but 80% of them express SSTR2 too. Octreotide is administered sc. or by iv. route usually 200 µg twice daily. The slow-release formulation of octreotide (Sandostatin LAR), 10-30 mg is administered once every 4 weeks. *Sideris et al.* have found that stable disease was achieved in 86% of patients treated with sc. octreotide and 88% of patients treated with im. octreotide LAR in non-differentiated functioning and non-functioning GEP-NET (19). *Rinke et al.* in PROMID study confirmed the antitumor effect of octreotide in 85 patients with well-differentiated metastatic GEP-NET of the midgut, median time to tumour progression was extended (14.3 month) with octreotide LAR, stable disease was observed in 67 vs. 37% of treated patients vs. placebo (20).

Acromegaly

Acromegaly is caused by a benign tumour in the pituitary gland with increased secretion of GH and IGF-1 by the liver resulting in excessive proliferation of bone, cartilage and soft tissues. Transsphenoidal surgery is the first line treatment, but in patients with large adenomas (>20 mm) or high GH levels presurgical treatment is recommended. *Giustina et al.* have shown that octreotide LAR reduce tumour volume by 66% (21). Moreover octreotide therapy relieves symptoms of the tumour as headache, fatigue, joint pain, perspiration in 70% of patients with acromegaly (3). Good response is achieved in patients with high tumour expression of SSTR2 (22).

Portal hypertension, variceal bleeding

Portal hypertension results from increased resistance and increased flow of portal blood. Variceal haemorrhage is the most serious complication of portal hypertension. Guidelines recommend use of somatostatin analogues, such as octreotide as adjuvant therapy for the control of variceal haemorrhage: intravenously 1 µg/kg IR octreotide, followed by 1 µg/kg/hrs continuous infusion for 1 to 5 days, but at least the next 24 hrs after stop of bleeding. Octreotide acts by inhibiting glucagon, decreasing hepatic vein pressure and portal blood flow.

Chandok et al. used octreotide LAR in 25 patients with portal hypertension and small oesophageal varices (10, 30 mg or saline), but they have not found significant difference in hepatic vein pressure gradient compared to the control groups (23).

Primary intestinal lymphangiectasia (PIL)

PIL is a rare disorder characterized by dilated lymph vessels in the mucosa and submucosa of small intestine. Clinical symptoms are mild to moderate peripheral oedema, moderate to severe diarrhoea, abdominal mass, malabsorption syndrome, chylous ascites and iron deficiency anaemia. Management of the disease is not easy, low-fat diet with medium-chain triglycerides are important, steroids and antiplasmin therapy have been used in some cases (24). *Ballinger and Farthing* reported first the efficacy of octreotide in one PIL patient (25), the mechanism of action is based on splanchnic vasoconstriction, inhibition of vasoactive peptide, reduction in intestinal absorption of fats. *Sari et al.* studied the long-term safety of octreotide in 6 children (26). *Suehiro et al.* reported a case of a 63 years old patient with PIL treated successfully with octreotide LAR (27). Chylous ascites of different origins (postoperative and acute pancreatitis induced) was also successfully treated with octreotide (28).

Paraneoplastic syndromes

Octreotide could also be used in rare tumours as ectopic ACTH secreting tumours, in Cushing syndrome, oncogenic osteomalacia, in some NET secreting parathyroid hormone-related peptide and ectopic acromegaly caused by GHRH (growth hormone releasing hormone) overproduction (10).

Future possibilities

Octreotide sc. depot injection is a new analogue based on liquid-lipid-crystal formulation which provides a greater bioavailability for the drug and easier use for patients by prefilled syringes (29).

Oral octreotide (Octreolin) was used in a preliminary Phase III trial in patients with acromegaly, 65% of patients reached biochemical control of the disease (30).

Pasireotide was used in refractory and octreotide resistant patients providing relief of symptoms in 27% of patients (31). In a Phase III trial using pasireotide LAR vs high-dose octreotide LAR (40 mg) in 110 patients with advanced

GEP-NET, effect of pasireotide was not superior to octreotide LAR (32).

Radiolabelled octreotide (177Lu-DOTATATE: *Lutathera*, a conjugate consisting octreotate radiolabelled with 177Lu) has been used in patients with midgut GEP-NET vs. 60 mg octreotide LAR in a Phase III study. Fewer patients with radionuclide therapy have disease progression as compare to use of octreotide LAR (23 vs. 64 patients) (33).

Conclusions

First generation somatostatin analogues are useful in treating acromegaly, carcinoid syndrome caused by different GEP-NET, variceal haemorrhage and also in some rare cases as primary intestinal lymphangiectasia, rare tumours or cyhlous ascites. In octreotide resistant cases new formulation as lanreotide and pasireotide could be used.

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