Drug Review

OCTREOTIDE IN GASTROENTEROLOGY

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KEY WORDS :

A peptide inhibiting the release of growth hormone was originally detected accidentally by Krulich et al [1] in 1968 and was called somatostatin. Shortly after its isolation, somatostatin was demonstrated to have a wide variety of biological effects. However, the therapeutic potential of somatostatin was limited by its short biological half life of less than 3 minutes and the post infusion rebound hypersecretion of hormones. Not surprisingly, protein chemists began to synthesize analogues of somatostatin with a similar spectrum of action but with a much longer biological half life. The first of these analogues to be freely available for clinical use was an octapeptide SMS 201-995 known as octreotide. Two other cyclic analogues with slightly different activity profiles - vapreotide and lanreotide - are being tested in clinical trials in Europe. At present over 30 synthetic analogues are available but only octreotide has been extensively investigated in a wide variety of gastrointestinal indications.

Pharmacokinetics

Octreotide is an octapeptide in which the four amino acid sequence essential for the biological activity of the native hormone is retained. However, incorporation of N-phenylalanine, L-terminal amino alcohol, D-tryptophan and a cysteine bridge makes the molecule very resistant to metabolic degradation [2]. The increased resistance of octreotide to metabolic degradation compared to somatostatin results in much longer metabolic half life. Since octreotide is poorly absorbed following oral administration it is administered by either in-

travenous or subcutaneous route. Both routes are well tolerated and have a similar bioavailability. Serum concentration of octreotide increases linearly with dose. The disposition of octreotide is biphasic. There is a first disposition phase with a half life of 9 to 13 minutes and a terminal distribution phase with a half life of 90 minutes, which is 30 times longer than that of somatostatin [3]. Octreotide is largely metabolised by the liver. Consequently in cirrhotic patients the plasma half life of octreotide is increased and in these patients the dosage regimens should be modified to avoid accumulation of octreotide. Similarly in patients with severe renal impairment plasma clearance of octreotide is reduced by 50 per cent and in these patients too octreotide dose should be carefully titrated.

Side effects associated with octreotide are mainly local or gastrointestinal. Local reactions include pain and burning at the site of injection and these rarely last more than 15 minutes. Gastrointestinal side effects include anorexia, nausea, vomiting, cramp like abdominal pain, diarrhoea and steatorrhoea.

Mechanism of action

The various actions of somatostatin are mediated through specific membrane receptors. Five subtypes of human somatostatin receptors have been cloned and characterised. Octreotide binds with high affinity to somatostatin receptor subtype 2 and subtype 5 and with moderate affinity to subtype 3. Subtype 3 receptor is found in the pancreas and subtype 5 in the small intestine. The gastroin-

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testinal effects of octreotide are inhibitory to the azygous blood flow, gastric secretions, splanchnic hemodynamics, pancreatic secretions, intestinal motility and all gastroenteropancreatic (GEP) endocrine secretions.

Clinical use

1. *GEP endocrine tumours:* The various peptide hormones produced by GEP endocrine tumours can cause a number of characteristic clinical symptoms. The current treatment modalities for these tumours, i.e. surgery, hepatic artery embolisation, cytotoxic chemotherapy and α -interferon are merely palliative and of relative short lived efficacy. Treatment with octreotide allows symptom free periods for patients with hypersecretory disorders by inhibiting hormone output from the tumours and preventing hormone action on the target tissue. Clinical improvement occurs in 50 to 85 per cent patients during treatment with 150 to 300 microgram of octreotide per day [4].
2. *Diarrhoea:* Octreotide prolongs the gastrointestinal transit time, decreases endogenous fluid secretion in the jejunum and stimulates the intestinal absorption of water and electrolytes. In secretory diarrhoeas, in patients with ileostomies, short bowel syndrome and radiation enteritis octreotide in a dose of 50 to 500 microgram per day has been found to be useful [5]. In patients with AIDS related diarrhoea octreotide induces a significant response, thereby improving the quality of life [5].
3. *Variceal bleeding:* Octreotide decreases the inflow of blood to portal system by constricting the splanchnic arterioles and significantly reduces intravariceal pressure. Octreotide in a dose of 50 microgram intravenous bolus followed by a continuous infusion of 50 microgram per hour for 48 hours and emergency sclerotherapy have been found to be equally effective in the control of variceal bleeding [6]. This study suggests that octreotide can be administered when injection sclerotherapy is not available and is probably also useful for recurrent bleeding after sclerotherapy.
4. *Pancreatic and gastrointestinal fistula:* Octreotide inhibits exocrine pancreatic secretions

and thereby reduces the fluid production by pancreatic fistulas. Various studies have shown a higher rate of closure of pancreatic fistulas or at least a significant decrease in the fistula output [7,8]. In patients with gastrointestinal fistulas octreotide has been shown to decrease the fistula output by 50 to 80 per cent and accelerate the closure of fistula in 80 per cent of these patients [5].

5. *Acromegaly:* Suppression of growth hormone in response to octreotide in patients with acromegaly is dependant on the number of receptors for somatostatin analogues in the tumour. Initial dose of octreotide is 3 daily subcutaneous injections of 100 microgram each which can be later increased upto 600 microgram per day [9]. Symptoms like headache, excessive perspiration and joint pains respond well to octreotide. Patients who have undergone an unsuccessful operation or are awaiting the therapeutic effect of irradiation are candidates for treatment with octreotide.

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