Long acting somatostatin analogue: Clinical potential for gastrointestinal disease

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ABSTRACT: Native somatostatin is found throughout the gastrointestinal tract and has a wide variety of biological actions. Nevertheless, its short biological half-life and limited stability necessitate its use via continuous parenteral infusion and, thus, limits its therapeutic usefulness. The development of long acting somatostatin analogues have lead to a re-examination of the therapeutic usefulness of somatostatin in gastrointestinal disease. Somatostatin analogues appear most beneficial in preventing symptoms associated with neuroendocrine tumours. In addition, case controlled studies exist to demonstrate somatostatin analogue effectiveness in treatment of gastrointestinal hemorrhage, pancreatic fistula, pancreatitis, short bowel syndrome and dumping syndrome. **Can J Gastroenterol 1989;3(2):77-81**

Key Words: *Diarrhea, Dumping syndrome, Fistula, Hemorrhage, Intestine, Pancreatitis, Short bowel syndrome, Somatostatin analogue*

L'analogue à effet prolongé de la somatostatine: Potentiel clinique pour les maladies gastrointestinales

RESUME: Le somatostatine naturelle se trouve tout le long de la voie gastrointestinale et ses actions biologiques sont multiples et variées. Néanmoins, sa demi-vie biologique courte et sa stabilité limitée requiert qu'on l'utilise en perfusion parentale continue, ce qui limite son utilité thérapeutique. La mise au point d'analogues à effet prolongé a conduit à une réexamen de l'utilité thérapeutique de la somatostatine dans les affections gastrointestinales. Les analogues de la somatostatine semblent particulièrement utiles dans la prévention des symptômes associés aux tumeurs neuroendocrines. De plus, des études de cas contrôlées ont démontré l'efficacité des analogues de la somatostatine dans le traitement des hémorragies gastrointestinales, des fistules pancréatiques, des pancréatites, du syndrome de l'intestin court et du syndrome de chasse.

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NATIVE SOMATOSTATIN IS A CYCLIC tetradecapeptide found throughout the gastrointestinal tract and pancreas in nerve endings and mucosal neuroendocrine cells (1-5). Somatostatin is found in the highest concentration in gastric fundus and antrum, pancreas and duodenum, in decreasing concentrations from proximal to distal small intestine and rarely in the colon (6). Somatostatin-14 is the principal form released from the stomach. Somatostatin released from small intestinal mucosa is predominantly somatostatin-28, whereas in nonmucosal small intestinal neural structures, it is predominantly somatostatin-14. As one of the regulatory peptides of the digestive tract, it has a wide variety of biological actions. It has been shown to reduce intestinal motility (7,8), enteric hormone release (9,10), splanchnic bloodflow (11), and inhibit secretion by the gastric antrum (12), pancreas (9) and the small and large intestines (13,17).

These properties of native somatostatin have resulted in its being considered as an antidiarrheal agent since 1973 when Brazeau and colleagues (18) isolated, sequenced and synthesized the peptide from bovine hypothalamic extract. The peptide was initially termed growth hormone release inhibiting factor (GHRIF) but is now commonly known as somatostatin.

Clinically, native somatostatin has been most effective as an antidiarrheal in hormonally mediated secretory diarrheas, including those produced by tumours secreting vasoactive intestinal peptide (VIPoma) (19), 5-hydroxytryptophan (carcinoid syndrome) (20-22), gastrin (Zollinger-Ellison syndrome) and calcitonin (metastatic islet cell carcinoma) (24). In nonhormonally mediated diarrhea, however, it has been less effective, failing to alter diarrhea induced by cholera toxin (25).

Although native somatostatin has been shown to reduce stool output in a patient with short bowel syndrome, this may have occurred because somatostatin suppressed the elevated blood levels of glucagon, gastrointestinal polypeptide and pancreatic polypeptide (26). Unfortunately, the short biological half-life (1 to 3 mins) and limited stability of native somatostatin necessitate its use via continuous parenteral infusion and thus limit its therapeutic usefulness.

Recently, an octapeptide long acting somatostatin analogue, SMS 201-995, (Sandostatin; Sandoz Inc) has been synthesized from the biologically active pharmacophone (Figure 1) (27). Beginning with the isolation of native somatostatin-14 and the knowledge of the minimal fragment needed for biological action, serveral long acting somatostatin analogues have been synthesized (28), although the most effective remains SMS 201-995.

This analogue contains D-phenylalanine at one end and an alcohol derivative of threonine at the other, making it resistant to enzymatic degradation. The substitution of D-tryptophan for L-tryptophan in position 8 further reduces degradation and enhances the long acting effect. This agent has been shown to be more potent and longer acting than native somatostatin and can be administered subcutaneously (27-29).

In vitro, SMS 201-995 has an antisecretory effect on intestinal fluid and electrolyte transport similar to that of native somatostatin (29). SMS 201-995 inhibits electrogenic anion secretion and stimulates neutral sodium and chloride absorption and thus has a potential for a potent antidiarrheal agent (29). The antidiarrheal effect of SMS 201-995 is approximately 60 times more potent than native somatostatin and does not exhibit the tachyphylaxsis seen with native somatostatin.

POTENTIAL GASTROINTESTINAL THERAPEUTIC APPLICATIONS

Clinical studies with somatostatin analogue have, for the most part, been anecdotal, and double-blind prospective studies are required before the full therapeutic benefit of this analogue can be determined. Although SMS 201-995 does not demonstrate the tachyphylaxsis seen with native somatostatin, recent reports have described relapse of diarrhea weeks to months after initial response to SMS 201-995 (30,31). This apparent desensitization or down regulation to SMS 201-995 remains to be explained.

Diarrhea due to neuroendocrine tumours: Somatostatin analogue, SMS 201-995, has been used successfully to control symptons, including diarrhea, of a vast array of neuroendocrine tumours of the gut. In gastrinomas, circulating gastrin levels are reduced, significant suppression of acid secretion takes place and diarrhea is markedly reduced. In some cases, regression of hepatic metastases have been identified (32-35).

In watery diarrhea, hypokalemia, achlorhydria syndrome, vasoactive intestinal peptide and its homologue, peptadine histidine isoleucine, are markedly reduced with the change in net intestinal secretion to net absorption and a significant reduction in stool weight and frequency, with resultant independence from intravenous fluid requirements (34,36-41). In only one of these cases of VIPomas did a decrease in diarrhea continue despite increased vasoactive intestinal peptide levels in the face of further metastases (36).

In the carcinoid syndrome, somatostatin analogue has significantly reduced both flushing, unstable angina and diarrhea by reducing circulating serotonin and kinin levels (33,42-44). During metastastic medullary carcinoma of the thyroid, somatostatin analogue alleviated the symptoms of flushing and diarrhea associated with elevated calcitonin levels but did not alter the course of the disease (35,44,45).

Somatostatin analogue has also produced an euglycemic state in insulinoma and glucagonoma syndromes (33). In the glucagonoma syndrome, somatostatin analogue therapy has been used to ameliorate the migratory necrolytic dermatitis (33).

In summary, somatostatin analogue which can be administered to an outpatient on an intermittent basis, is proving invaluable in patients with rare, neuroendocrine secreting tumours by controlling the life threatening diarrhea and vasomotor responses. Furthermore, the potential exists for its use intraoperatively during surgical manipulation of neuroendocrine tumours when large

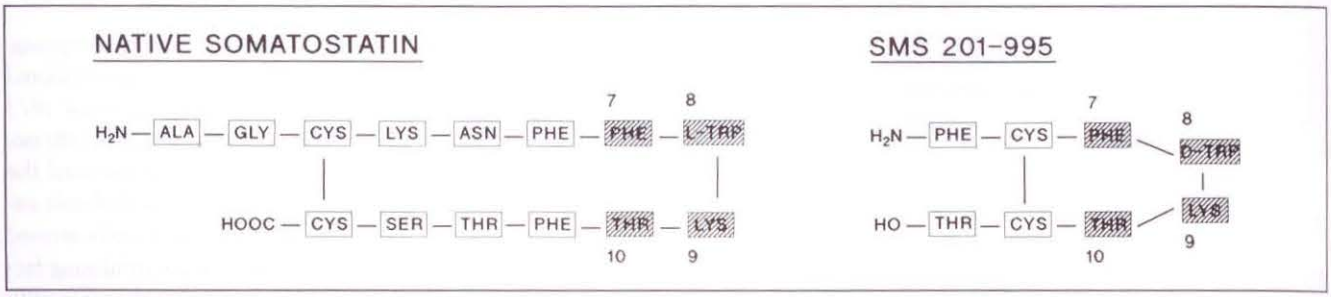

Figure 1) *Structural relationship of native somatostatin-14 and the synthetic long acting somatostatin analogue, SMS 201-995. The essential pharmacophore is the PHE$_7$-TRP-LYS-THR$_{10}$ fragment. Substitution of D-tryptophan for L-tryptophan at position 8 reduces enzymatic degradation*

amounts of biologically active peptides can be released following surgical manipulation of the tumour. The mechanism of action of somatostatin analogue in controlling symptoms of neuroendocrine tumours has not been elucidated. However, it appears to be a consequence of reduced circulating amine and peptide levels.

Diarrhea with nonendocrine etiology: In patients with diarrhea not attributable to neuroendocrine tumours, treatment results with somatostatin analogue have been less dramatic. In diarrhea due to cholera enterotoxin (46), ileostomy (47), inflammatory bowel disease (48) and diabetic diarrhea (unpublished observations), somatostatin analogue has not been effective. Nevertheless, the somatostatin analogue has been described to control severe diarrhea as a consequence of infant secretory diarrhea (49, 50), cryptosporidia infection in the acquired immune deficiency syndrome (55-53), nonsecretory ileostomy diarrhea (54,55) diabetic diarrhea (34,56) and in 50% of cases with idiopathic secretory diarrhea (32). Since hormone levels were not measured in many of these reports, it is difficult to determine whether the effect of somatostatin analogue was a consequence of reduced hormonal output or a direct antidiarrheal action on the intestine.

In nonneuroendocrine mediated diarrhea, the effect of somatostatin analogue appears variable and may relate to the inability to achieve therapeutic drug levels at the enterocyte level.

Gastrointestinal hemorrhage: Control of bleeding by native somatostatin therapy has been reported in both nonvariceal and variceal hemorrhages in a small number of studies (57). Studies to examine the effect of somatostatin analogue on gastrointestinal hemorrhage are even fewer and the results are conflicting. In treatment of relapsing bleeding peptic ulcers in a patient with Zollinger-Ellison syndrome, it was found to be more potent than native somatostatin in reducing gastric acid secretion and in reducing intestinal mucosal bloodflow for a substantially longer period and resulted in cessation of bleeding in eight of 10 patients (58,59).

Somatostatin analogues demonstrated a dose dependent effect on the mortality, incidence and intensity of cysteamine-induced duodenal lesions in rats (60). In contrast, somatostatin analogue did not demonstrate splanchnic vasoconstrictive effects in anesthetized pigs despite adequate serum levels (61) and inhibited naturally occuring vasopressin secretion during gastrointestinal hemorrhage (62).

With the present day effectiveness in safely suppressing gastric acid production and with the advent of therapeutic endoscopy, it is unlikely that somatostatin analogues will replace existing therapy for gastrointestinal hemorrhage.

Pancreatic fistulas: Somatostatin analogues have been demonstrated to potently inhibit exocrine pancreatic secretion, bicarbonate, protein and fluid in a dose dependent fashion (63). The treatment of pancreatic cutaneous fistulas with somatostatin analogues has been reported in nine patients (64-69). In each of these cases, fistula output was consistently reduced during somatostatin analogue administration. Nevertheless, in only three of these patients was it documented that fistulas closed as a consequence of somatostatin analogue administration.

Pancreatis: In a controlled, double-blind, multicentre trial, native somatostatin in the treatment of acute pancreatitis demonstrated no advantage in either the course of the disease or the mortality (70). Recently, somatostatin analogues have been identified to have a cytoprotective effect on pancreatic, bronchial and gastric epithelium (71). The mechanism leading to tissue protection has not been clarified, although stabilization of cell membrane as well as changes in amino acid sequence may play a role.

Somatostatin analogues administered prior to various forms of experimental pancreatitis have improved survival, demonstrated improved histological healing and reduced serum levels of lipase and amylase (72-74). Once again, the mechanism of this effect during pancreatitis is unknown but may relate to inhibition of pancreatic enzyme secretion. Recently, Conway and colleagues (75) demonstrated in dogs that somatostatin analogue produces a prompt and sustained decrease in pancreatic bloodflow without alteration in systemic hemodynamics.

Somatostatin analogues do not presently have a role in the treatment of acute pancreatitis outside the clinical research centre. Nevertheless, their role in preventing pancreatitis following endoscopic or surgical manipulation of the pancreas remains to be determined.

Short bowel syndrome: Although Dharmsathaphorn and colleagues (76) demonstrated, as early as 1982, that native somatostatin decreases diarrhea in patients with short bowel syndrome, only a single case report of a child exists to demonstrate the use of long acting somatostatin in controlling ileal output as a consequence of the short bowel syndrome (77).

Dumping syndrome: Since somatostatin inhibits vasoactive peptides and amines and prevents massive fluid secretion into the intestinal lumen, the potential therapeutic effect for the treatment of dumping syndrome exists.

The effect of somatostatin analogue in 10 patients with retractable early dumping and seven patients with severe late dumping has been examined (78,79). In both early and late dumpers, somatostatin analogue improved symptoms and breath hydrogen excretion, indicating slowing of gastrointestinal motility. Unfortunately, the diminshing rate of gastric surgery for peptic ulcer disease may make a large, double-blind study to examine the effect of somatostatin analogue on gastric dumping difficult to carry out.

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