Management of the hormonal syndrome of neuroendocrine tumors

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Abstract

Gastroenteropancreatic neuroendocrine tumors (GEP/NET) are unusual and rare neoplasms that present many clinical challenges. They characteristically synthesize store and secrete a variety of peptides and neuroamines which can lead to the development of distinct clinical syndrome, however many are clinically silent until late presentation with mass effects. Management strategies include surgery cure and cytoreduction with the use of somatostatin analogues. Somatostatin have a broad range of biological actions that include inhibition of exocrine and endocrine secretions, gut motility, cell proliferation, cell survival and angiogenesis. Five somatostatin receptors (SSTR1-SSTR5) have been cloned and characterized. Somatostatin analogues include octreotide and lanreotide are effective medical tools in the treatment and present selectivity for SSTR2 and SSTR5. During treatment is seen disapperance of flushing, normalization of bowel movements and reduction of serotonin and 5-hydroxyindole acetic acid (5-HIAA) secretion. Telotristat represents a novel approach by specifically inhibiting serotonin synthesis and as such, is a promising potential new treatment for patients with carcinoid syndrome. To pancreatic functionig neuroendocrine tumors belongs insulinoma, gastrinoma, glucagonoma and VIP-oma. Medical management in patients with insulinoma include diazoxide which suppresses insulin release. Also mTOR inhibitors may inhibit insulin secretion. Treatment of gastrinoma include both proton pump inhibitors (PPIs) and histamine H2 – receptor antagonists. In patients with glucagonomas hyperglycaemia can be controlled using insulin and oral blood glucose lowering drugs. In malignant glucagonomas smatostatin analogues are effective in controlling necrolytic migratory erythemia. Severe cases of the VIP-oma syndrome require supplementation of fluid losses. Octreotide reduce tumoral VIP secretion and control secretory diarrhoea.

Key words: neuroendocrine tumors, hormonal syndrome.

Introduction

Neuroendocrine tumors of the gastrointestinal tract and pancreas may produce one of several peptide hormones. These tumor products are released into the circulation and are subsequently transported to the various target organs on which they exert their action. Generally, this excessive hormone production will be reflected by a characteristic clinical syndrome. A good therapeutic approach in patients with an endocrine

tumor of the gastrointestinal tract and excessive hormonal secretion is to control both problems in tandem [1–3]. Symptomatic medical therapy of these disorders currently consists of biotherapy using somatostatin analogues and/or interferons, or other symptomatic therapies aimed at treatment and correction of tumor-related deficiencies or disorders [4, 5].

Somatostatin analogues

Somatostatin is a small cyclic peptide hormone, which is present in the human body in the molecular forms SRIF-14 (consisting of 14 amino acids) and SRIF-28 (consisting of 28 amino acids) [6]. Somatostatin has diverse biological effects in different organ systems. These effects are mediated through specific somatostatin receptors (ssts) on the target tissue [7]. The presence of ssts has also been demonstrated throughout the human gastrointestinal mucosa and pancreas. The gastrointestinal transit time, secretion of intestinal hormones by intestinal endocrine cells, the peptide-induced secretion of intestinal fluid and the resorption of intestinal fluid can be inhibited through the action of somatostatin on these receptors [8]. Ssts belong to the family of G-protein coupled receptors. Five different sst subtypes have been cloned and characterized. These receptor subtypes have been named sst1-5. Sst binding studies, somatostatin mRNA determination, and/or sst immunohistochemistry have identified abundant expression of ssts in endocrine tumors of the gastrointestinal tract and pancreas [9, 10]. In general, sst expression varies between patients and between tumors, but sst2 predominance is found in more than 80% of these tumors [11, 12]. Apart from the usefulness as a tumor marker, the expression of ssts by human tumors has other important clinical implications, such as inhibition of tumor peptide hormone secretion by somatostatin analogues and inhibition of tumor growth by somatostatin. For therapeutic purposes, structural analogues of somatostatin have been synthesized. Octreotide acetate (Sandostatin) is a synthetic octapeptide, which can be administered by multiple (2–3 times daily) subcutaneous (*s.c.*) injections, or by continuous s.c. infusion and by the intravenous (*i.v.*) route, either as a single injection or as a continuous infusion over many hours or days. A slow-release depot intramuscular (*i.m.*) formulation of octreotide (Sandostatin LAR) which has to be administered every 4 weeks is also available [13]. Another cyclic analog, lanreotide (Somatuline) has become available, either as a slow-release *i.m.* depot formulation (Somatuline PR) which needs to be administered every 10–15 days, or as a slow-release deep *s.c.* depot preparation, which has to be administered once every 4 weeks (Somatuline Autogel) [14]. Octreotide and lanreotide have comparable binding profiles and bind with a high affinity to sst2 and sst5, show a low affinity to sst3, and no affinity to sst1 and sst4 (Table I). Tumors and metastases that bear predominately sst2, or sst5, can be visualized *in vivo* after injection of radiolabelled octapeptide analogues [15, 16]. Somatostatin analogues have proven antiproliferative effects. The CLARINET study was a randomized, double-blind, placebo-controlled, multinational study of the somatostatin analogue lanreotide in patients with advanced well-differentiated or moderately nonfunctioning, somatostatin receptor positive neuroendocrine tumors of grade 1 or 2 (Ki67 below 10%). The tumors originated in the pancreas, midgut, hindgut or were of unknown origin. Lanreotide treatment, as compared with placebo, was associated with significantly prolonged progression-free survival (median not reached) vs. a median of 18.0 months in the placebo group [17–20].

Interferon-α

Interferon is an antiviral and antitumor agent. Five interferon classes have been described. Recombinant interferon-α2a (Roferon A) and interferon-α2b (IntronA) are the most frequently used interferons in the treatment of neuroendocrine tumors of the gastrointestinal tract and pancreas [21]. The effects of interferon-α are mediated

Table I. Somatostatin congener binding affinities to sst subtypes

Variable	SST				
	SST1	SST2	SST3	SST4	SST5
Somatostatin 14	0.93–2.30	0.20–0.30	0.60–1.40	1.50–1.80	0.30–1.40
Octreotide	280–1140	0.40–0.60	7.10–34.5	850–1000	6.30–7.00
Lanreotide	180–2330	0.50–0.80	14.0–107	230–2100	5.20–17.0
Pasireotide	9.30	1.00	1.50	100	0.20
BIM-23A760	662–853	0.03	52.0–160	1000	3.10–42.0

Affinity to sst = IC50 value (Nm) = (Mean ± SEM).

via the interferon type 1 receptors. The antitumor effects of interferon-α have been proposed to occur through antiproliferative, apoptotic, differentiation and anti-angiogenic immunomodulatory mechanisms [22]. Another proposed effect of interferon-α is the induction of fibrosis within liver metastases [23].

Carcinoid syndrome

Carcinoids of the small intestine (previously designated as midgut carcinoids) are the most likely to cause carcinoid syndrome. After metastasizing to the liver, bioactive amines may reach the systemic circulation and carcinoid syndrome ensues. These small intestinal carcinoids account for 75–90% of all cases of carcinoid syndrome [24].

Medical therapy of carcinoid syndrome

Treatment of carcinoid syndrome with somatostatin analogues

The use of somatostatin analogues to block the release of vasoactive peptides and amines is the mainstay for the control of the symptoms of carcinoid syndrome. Medical therapy for carcinoid syndrome usually consists of either 300–1500 µg *s.c.* octreotide (Sandostatin), injected in total daily dosages; 20–60 mg slow release *i.m.* octreotide (Sandostatin LAR), injected every 2–4 weeks; 30 mg slow release *i.m.* lanreotide (Somatuline PR), injected once every 2 weeks; or 90–120 mg slow release *s.c.* lanreotide (Somatuline Autogel), injected once monthly. This medical therapy usually results in the complete amelioration of flushing episodes in 60% of patients, while in > 85% the frequency and/or severity of the flushing periods can be reduced to < 50%, leading to a significantly improved quality of life. A significant improvement in the quality of life (QoL) and in the global health status was observed after therapy with somatostatin. The patients completed the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 before and after therapy. The score increased significantly after therapy to a mean value of 78.2, up from 69 (scale range 0–100). Furthermore, improvement was observed in the emotional and social aspect of life [25]. Disappearance of diarrhea (less than four bowel movements per day) is observed in > 30% of patients, and > 50% improvement in > 75% of patients with this therapy. Biochemically, a significant reduction of the increased urinary excretion of the serotonin breakdown product 5-hydroxyindoleacetic acid (5-HIAA) has been found in > 50% of patients [25, 26]. In addition, objective antineoplastic effects have been recently reported with this therapy [27]. However, insensitivity to somatostatin analogues may develop in time [28]. Octreotide acetate comes in two forms: an aqueous (*s.c.* or *i.v.*) immediate release product, and a sustained release (long acting repeatable – LAR) form. The aqueous form is widely used initially in a long-term treatment plan as a test compound for the tolerability of the LAR form. To test the safety and efficacy, and discover any possible allergic reactions in individual patients, somatostatin analogue therapy should be initiated with, for example, short-acting octreotide (100 µg *s.c.* 2–3 times daily). The short-acting form of octreotide is also commonly used following the administration of the sustained-release form, as a rescue injection for periods when the patient is exhibiting breakthrough or recalcitrant symptoms [29]. In the past, ultrahigh doses of somatostatin analogues have shown beneficial effects. Ultrahigh-dose lanreotide therapy (5 mg *s.c.* three times a day) in patients with metastatic GEP/NET shows improvement in control of both symptoms and proliferation in at least some patients refractory to conventional therapies. High-dose somatostatin analogue treatment showed an antiproliferative effect in a study including patients with neuroendocrine tumors. To explore this therapeutic strategy further, a study was performed on the effect of high-dose formula of octreotide (160 mg *i.m.* every 2 weeks) in midgut carcinoid patients. In this group of patients octreotide therapy managed to improve symptoms and stabilize hormone production and tumor growth in 75% of the patients [30, 31]. Furthermore, it has been shown that the measurement of octreotide blood levels with a highly sensitive and specific octreotide assay might be helpful. Octreotide long acting repeatable (LAR) is widely used for the control of symptoms of functional neuroendocrine tumors. At dose of 30 mg/mo. up to 40% of patients require subcutaneous octreotide administration. Octreotide acetate binds to the sst2 receptor with an affinity of 1×10^{-9} mol/l when the concentration in the blood is 10 000 pg/ml. Octreotide concentration in serum can be determined by radioimmunoassay. Frequent measurement of octreotide levels may be useful to guide octreotide therapy in patients with poorly controlled symptoms or those patients experiencing tumor growth [27]. Side-effects usually subside within a few weeks, but can include abdominal discomfort, delayed gastric emptying, bloating, and sometimes fat malabsorption steatorrhea. Side-effects which can develop later are gallstones and persistent steatorrhea, which results in fat soluble vitamin D deficiency, calcium malabsorption and vitamin B_{12} deficiency [32–34].

Pasireotide (S0M 230) is a novel multi-ligand with a high binding affinity for sst subtypes 1, 2, 3 and 5 (sst1, sst2, sst3, sst5). A phase II clinical

trial showed that this drug was effective in controlling the symptoms of diarrhea and flushing in 27% of patients with small bowel carcinoids who were refractory or resistant to the standard therapeutic dose of octreotide [35, 36]. BIM-23A760 is another compound being tested which targets sst2 and the dopamine D2 receptors [37].

Interferon-α treatment of carcinoid syndrome

The interferons interferon-α2a and interferon-α2b (IFN) bind to specific interferon receptors on neuroendocrine tumor cells. The human interferon receptor (IFNAR) is comprised of subunits IFNAR1 and IFNAR2. Binding of IFN to its receptors mediates the antiviral and antiproliferative effect [38]. After binding of IFN to its receptor, a signal transduction cascade is activated, leading to the transcription of multiple tumor suppressor genes. IFN-α acts on specific enzymes, such as 2',5'-oligoadenylate (2-5A) synthetase and p-68 kinase, leading to the degradation of peptide hormones and inhibition of protein synthesis. In neuroendocrine tumors, the indications for interferon treatment are roughly similar to those of somatostatin congeners except in a carcinoid crisis. Interferon-α may, therefore, be used as a second line approach for symptomatic therapy. Symptomatic response and quality of life improvement have been observed in approximately 40% of patients, with a greater beneficial effect on flushing than with diarrhea. Partial tumor regression occurred in 5.7%, and stabilization of serotonin secretion and tumor growth in 44.8% of patients with midgut carcinoid tumors [38]. The reported rate of tumor stabilization is considered to be slightly, but not significantly, higher than with somatostatin congeners. Faiss *et al.* reported a multicenter prospective randomized study showing that interferon α and somatostatin analogues, or a combination of the two, had comparable antiproliferative effects in neuroendocrine gastroenteropancreatic tumors [39]. Recombinant interferon-α2a and interferon-α2b are the most widely used. There is essentially no difference in clinical responses between the different subtypes of interferon-α. However, lower response rates have been reported for interferon-α2a, which might be related to the development of neutralizing interferon antibodies. The recommended doses are 3–9 × 10^6 U *s.c.* every day or every other day. However, it is important to titrate the dose in each individual according to tolerance. The biochemical response varies from 15% to 45%. The combination of a somatostatin congener with interferon-α does not seem to significantly increase therapeutic efficacy [40, 41].

These results are very encouraging, but the treatment also has significant side effects which have to be managed by dose titration in each individual patient. The minor side effects of interferon-α are flu-like symptoms (which generally respond to paracetamol), anorexia and weight loss (60%), and fatigue (50%). Major side effects are bone morrow toxicity (31%), hepatotoxicity (31%), autoimmune disorders, depression and other mental disturbances. Polyethylene glycosylated recombinant interferons are available and have demonstrated fewer side effects and easier administration.

Other therapies for carcinoid syndrome

In patients with carcinoid syndrome, biotherapy with somatostatin congeners and interferon are the treatments of choice. Before the introduction of these drugs, opioids (opium tincture) and loperamide were the only useful drugs in controlling diarrhea, as they increase intestinal transit time. Blockade of serotonin receptors can also ameliorate diarrhea. LX1032 (telotristat etiprate) is designed to reduce serotonin production in patients with metastatic carcinoid tumors, thus relieving gastrointestinal and, possibly, other symptoms experienced by patients with carcinoid syndrome. Telotristat etiprate is an orally bioavailable, tryptophan hydroxylase (TPH) inhibitor with potential antiserotoninergic activity. Telotristat represents a novel approach by specifically inhibiting serotonin synthesis and, as such, is a promising potential new treatment for patients with carcinoid syndrome. TELESTAR was a double-blind phase 3 study that enrolled 135 patients with carcinoid syndrome which was not adequately controlled on SSA therapy. Top line results from TELESTAR showed that patients who added telotristat etiprate to the standard of care, somatostatin analog depot, at both 250 mg and 500 mg doses experienced a statistically significant reduction from baseline compared to placebo in the average number of daily bowel movements [42]. Diarrhea is not always the consequence of excessive hormonal secretion. It may deteriorate, or even start, after small bowel resection for a primary ileal carcinoid. In such cases, diarrhea can result from short bowel disease and/or bacterial overgrowth with the subsequent deconjugation of bile acids. Malabsorption steatorrhea can result from serotonin-induced hypermotility. In patients who have undergone a right hemicolectomy, medical interventions aim to reduce colonic bile acids (with bile acid sequestrants such as cholestyramine) and treat bacterial overgrowth using antibiotics. Fat absorption can be improved using pancreatic enzyme supplementation, especially in patients treated with high doses of somatostatin congeners. Some beneficial effects of blocking the histamine 1 and 2 receptors with a combination of somatostatin congeners have also been reported

[43]. Cyproheptadine has been shown to reduce diarrhea, but not flushing. It is a pan serotonin receptor blocker and is indicated in serotonin syndrome. Limitations include drowsiness at the recommended dose of 12 mg daily. A liquid form is available and can be titrated gradually. Pellagra is treated with niacin substitution [44]. Because flushing and diarrhea may be associated with particular precipitants, life style adjustments may be required: patients should avoid known precipitants such as alcohol, spicy foods, and strenuous exercise.

Peptide receptor radionuclide therapy (PRRT) of gastroenteropancreatic tumors

An individualized approach towards PRRT with somatostatin analogues has proven to be an effective (anti-tumor effects, progression-free survival and survival) and safe treatment for sst-positive, unresectable neuroendocrine tumors. Overexpression of somatostatin receptors (usually sst2) on NET cells and developments in radiolabeling of somatostatin analogues gave way to clinical studies on radiopeptide therapy (PRRT). Studies with the two most often used radiopeptides 90Y-DOTA-TATE and 177Lu-DOTA-TATE resulted in a response (complete or partial) in about 30% of treated patients [45–48]. Currently, the maximum tolerated dose is defined by the dose to the critical organs, kidney and bone marrow. In an attempt to increase the efficacy of PRRT, clinical trials that followed used β-emitting radionuclides, such as 90Y or 177Lu. Radionuclides emitting β-irradiation have greater therapeutic potential because of the higher linear energy transfer (LET). Also with β-emitting radionuclides, the emitted particle range exceeds the cell diameter. Furthermore, the ability to irradiate neighboring cells is an advantage in tumors which are characterized by a heterogeneous somatostatin receptor tissue distribution, with regions of high density next to regions which lack expression of the receptor. NETTER-1 was the first phase III multicentric, stratified, open, randomized, controlled, parallel-group study comparing 177Lu-DOTA-TATE with octreotide LAR (30 mg) in one arm and octreotide LAR (60 mg) in the second arm. The primary endpoint was progression-free survival (PFS) assessed per RECIST 1.1 criteria. In patients treated with radiolabeled somatostatin analogues median PFS was not reached. In patients treated with octreotide 60 mg median PFS was 8.4 months. It is also worth mentioning that the best results were obtained with the administration of a mixture of 90Y and 177Lu. It is very likely that future PRRT will be carried out in various forms of combinations with other, non-radionuclide mediated treatment modalities [49–55].

Pre- and peri-intervention strategies

Patients with midgut carcinoids are pre-treated with short- or long-acting somatostatin analogues to prevent an anesthesia-induced carcinoid crisis during surgery for tumor manipulation, chemoembolization or endoscopic procedures, or other interventions such as teeth extraction [56, 57]. Carcinoid tumors may express adrenoceptors. Spinal anesthesia can lead to reduced blood pressure and secondary release of catecholamines from the adrenals. For this reason, this type of anesthesia is not recommended for carcinoid patients. For the same reason, adrenergic drugs should be avoided. In cases of carcinoid crisis, the surgical or nonsurgical manipulation should be temporarily interrupted, blood volume should be substituted under the guidance of hemodynamic parameters and additional doses of *i.v.* octreotide in combination with *i.v.* glucocorticoids should be administered. For postoperative pain, epidural analgesia is preferred [58, 59].

Medical therapy of gastrinoma

Almost all the symptoms that patients with Zollinger-Ellison syndrome (ZES) present are due to the effects of the gastric acid hypersecretion which is characteristic of this disease (mean basal acid output is 6–7 fold higher than normal). Only late in the course of the disease do symptoms arise due to the gastrinoma itself, such as abdominal pain due to tumor invasion, bone pain, or gastric/biliary obstruction. The characteristic symptoms of acid hypersecretion are due to the peptic ulcer disease (PUD) which develops in these cases: gastroesophageal reflux disease (GERD); complications from the PUD/GERD; and diarrhea (either induced by gastric acid, or due to fat malabsorption steatorrhea). These symptoms can occur in 50–80% of patients.

In gastrinoma patients, gastric acid hypersecretion should, therefore, always be treated first. In the past, surgery (total gastrectomy) was the only effective means of controlling the effects of acid hypersecretion. At present in almost all patients gastric acid hypersecretion can be controlled medically except for the rare patient (< 1%) who cannot or will not take oral medications regularly. Both proton pump inhibitors (PPIs) and high dose histamine H2-receptor antagonists are effective, but PPIs are the drugs of choice because of their greater potency, longer duration of action and ease of administration [60]. Octreotide and lanreotide in dosages comparable to those used for carcinoid syndrome can also control acid hypersecretion in patients with gastrinomas and have a favorable outcome for prognosis and survival of patients [61, 62]. The combination of PPI and

somatostatin congeners offers an advantageous additive effect on gastric acid suppression.

Medical therapy of insulinoma

In patients with insulinomas, prolonged periods without glucose intake should be avoided by administering frequent carbohydrate-rich meals and/or by continuous glucose infusion either during the night or for a full 24-hour period [63, 64]. Octapeptide somatostatin analogues are of limited use in non-metastatic insulinomas, because less than 40% of these tumors express sst subtypes that bind these drugs [65–67]. Caution has to be taken in somatostatin analogue therapy in these patients, since hypoglycemia may worsen due to a more profound suppression of counterregulatory hormones, such as glucagon and growth hormone, than tumor-produced insulin.

The best approach is to determine whether there are sst2 and/or sst5 receptors on the tumor using [111In- DOTA] lanreotide, 111In-pentetreotide SPECT, or 68Ga-DOTANOC PET/CT. A subsequent test dose of short-acting octreotide can then be administered and blood glucose levels monitored over a period of 3–4 h. When these levels increase, the patient might benefit from one of the longer acting somatostatin congeners. β-receptor blockers may improve hypoglycemia by counteracting insulin sensitivity and insulin release. This needs careful consideration, as higher doses of β-blocker will mask symptoms of hypoglycemia. Diazoxide is effective in controlling hypoglycemia, acting to reduce insulin secretion by opening ATP-sensitive potassium (KATP) channels in insulinoma cells and has an extrapancreatic hyperglycemic effect of increasing gluconeogenesis. Daily dosages of 50–300 mg are generally used. Side effects are edema, renal impairment, and hirsutism. Thiazide diuretics enhance the effects of diazoxide by further antagonizing insulin release and counteracting edema from sodium retention. Verapamil, glucocorticoids and phenytoin, drugs which might all reduce insulin secretion, have also been used with variable success [68, 69].

Recent studies have demonstrated that abnormalities in the mammalian target of rapamycin (mTOR) pathway may be critical to the development of neuroendocrine tumors. Aberrant signaling upstream of mTOR in cancer cells then causes increased production of angiogenic growth factors and cell growth or proliferation, in addition to growth factor signaling. mTOR inhibitors may inhibit tumor growth by blocking signaling downstream of vascular endothelial growth factor (VEGF) and insulin-like growth factor receptors. In the fasting state, when mTOR is up-regulated, insulin production by the pancreatic β-cells is increased. Conversely, mTOR inhibition results in reduced insulin secretion by β-cells. Hyperglycemia and impaired glucose tolerance have, therefore, been reported as important side effects of the mTOR inhibitor everolimus [70]. In metastatic insulinomas mTOR inhibitors can reduce hypoglycemic episodes by reduction of the tumor mass, by reduction of the insulin secreting capacity, or by increasing insulin resistance [71, 72]. In the RADIANT-4 study everolimus was used for the treatment of advanced nonfunctional neuroendocrine tumors of the lung or gastrointestinal tract. Treatment with everolimus was associated with significant improvement in progression-free survival in patients with progressive lung or gastrointestinal neuroendocrine tumors. The safety findings were consistent with the known side-effect profile of everolimus. Everolimus is the first targeted agent to show robust anti-tumor activity with acceptable tolerability across a broad range of neuroendocrine tumors, including those arising from the pancreas, lung, and gastrointestinal tract [73, 74]. The clinical study RADIANT-3 showed the same effect in tumors of the pancreas [75, 76]. Other therapies directed at reducing tumor mass and, thereby, reducing insulin hypersecretion in patients with metastatic, malignant insulinomas are streptozotocin-based chemotherapy schedules and peptide receptor radiotherapy [77–79].

Medical therapy of glucagonoma

In patients with glucagonomas, hyperglycemia can be controlled using insulin or oral blood glucose lowering drugs [80, 81]. In both benign and malignant glucagonoma, octreotide and lanreotide are effective in controlling necrolytic migratory erythema, but less effective in the management of weight loss and diabetes mellitus, and ineffective in reducing the incidence of venous thrombosis, all common presenting conditions in glucagonoma. Aspirin therapy or low-dose heparin has been used for the prevention of thromboembolic disease. Topical or oral zinc therapy has been used to ameliorate necrotic migratory erythema [82]. Hypoaminoacidemia and mineral deficiencies should also be corrected.

Medical therapy of VIPom

Severe cases of the VIPoma syndrome (Verner-Morrison syndrome) often require intensive intravenous supplementation of fluid losses (often exceeding 10 l/day) and careful correction of electrolyte and acid-base abnormalities. Octapeptide somatostatin congeners reduce tumor VIP secretion by more than 50% and inhibit intestinal water and electrolyte secretion. By this mechanism, these drugs control secretory diarrhea in more than 50% of patients, and in another 25%, significant clinical improvement is attained. Glucocorticoids can also potentially improve diarrhea,

presumably by inhibition of VIP release and by enhancing sodium absorption in the intestinal tract. Further control of diarrhea can be acquired using loperamide and opiates [83]. Higher *i.v.* doses of octreotide may be required as the *s.c.* route may not be effective in patients with severe diarrhea.

Medical therapy of other hypersecretion syndromes

Cushing's syndrome in patients with ectopic adrenocorticotropin (ACTH) production can be controlled by somatostatin congeners, cabergoline, ketoconazole, metyrapone, etomidate, mifepristone, by combinations of these agents, or by laparoscopic biadrenalectomy [84–87]. Acromegaly in patients with ectopic growth hormone-releasing hormone (GHRH) production can be controlled by somatostatin congeners, cabergoline, growth hormone receptor blockers, or by combinations of these agents [88–90].

Humoral hypercalcemia of malignancy in patients with paraneoplastic parathyroid hormone related peptide (PTHrp) production can be controlled by somatostatin congeners and bisphosphonates, but not by cinacalcet [91, 92].

The future of medical therapy in patients with neuroendocrine tumors

Somatostatin binds with high affinity to all sst subtypes 1 to 5 (sst1-5), whereas the octapeptide congeners octreotide and lanreotide only bind with a high affinity to sst2 > sst3 > sst5. As detailed above, new classes of sst subtype-selective analogues have been developed. As every sst has distinct biological functions, these new congeners may prove valuable, both in the treatment of tumors that are sensitive to the currently available octapeptide analogues, and also in tumors that express sst subtypes other than sst2 and sst5. Pasireotide (S0M230) is a so-called universal somatostatin analogue with high affinity for sst1, sst2, sst3, and sst5 receptor subtypes [93].

New drugs which interact and cross talk with multiple receptor families are being developed. These sst subtype homo- or heterodimers may have properties which are distinct from the usual responses of individual receptors in terms of internalization, agonist-induced desensitization, and functional activity. BIM-23A760, an example of such a compound, targets sst2 and dopamine D2 receptors [94]. More sst antagonists are currently in pre-clinical development [95].

The cholecystokinin (CCK) and gastrin receptor subtype CCK2 (CCK-B, CCKBR) is expressed in some of the endocrine tumors of the gastrointestinal tract and pancreas (particularly in insulinomas) where subtype CCK1 (CCK-A, CCKAR) receptors can also be expressed. The expression of bombesin and gastrin-releasing peptide (GRP) receptor subtypes (neuromedin B receptor subtype (BB1), GRP receptor subtype (BB2), BB3 and BB4) has been studied in both endocrine and non-endocrine tumors of the gastrointestinal tract and pancreas. Gastrinomas preferentially express BB2, while ileal carcinoids often express BB1 [96].

Ongoing studies examine the expression of neurotensin receptors (such as receptor subtype NRT1), substance P (such as receptor subtype NK1), neuropeptide Y and other peptides in endocrine tumors of the gastrointestinal tract and pancreas. Analogues and/or antagonists of receptors detailed above may also interfere with the secretion of tumor products and peptides, resulting in a positive influence on tumor-related endocrine syndromes. High levels of glucagon-like peptide-1 (GLP-1) receptor expression in human insulinomas and gastrinomas provide an attractive target for imaging, therapy, and intraoperative tumor localization using exendin-4-diethylenetriaminepentaacetic acid (DTPA) conjugates [97–99]. LX1032, a drug which was designed to reduce diarrhea in patients with metastatic carcinoid tumors, is currently undergoing clinical trials.

Conflict of interest

The authors declare no conflict of interest.

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